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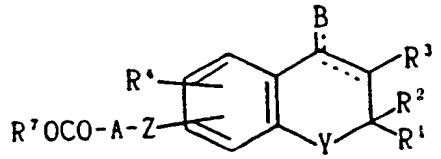
(54) Heterocyclic compounds, processes for producing them and pharmaceutical compositions comprising them.

(57) Novel heterocyclic compounds capable of lowering the uric acid levels in plasma and urine having the formula (I):



(I)

wherein R^2 and R^3 are independently hydrogen, lower alkyl, phenyl or substituted phenyl, or R^1 and R^2 may form a four to eight-membered carbon ring together with the carbon atom to which they are attached: R^3 is hydrogen or lower alkyl; R^4 is one or two radicals selected from a group consisting of hydrogen, halogen, nitro, lower alkyl, phenyl, substituted phenyl, $-OR^5$ and $-SO_2NR^6R^{6'}$; R^5 is hydrogen, lower alkyl, phenyl-substituted lower alkyl, carboxymethyl or ester thereof, hydroxethyl or ether thereof, or allyl; R^6 and $R^{6'}$ are independently hydrogen or lower alkyl; R^7 is hydrogen or a pharmaceutically active ester-forming group: A is a straight or branched hydrocarbon radical having one to five carbon atoms; B is halogen, oxygen, or dithiolane; Y is oxygen, sulfur, nitrogen or substituted nitrogen; Z is oxygen, nitrogen or substituted nitrogen; dotted line represents the presence or absence of a single bond, processes for their production and pharmaceutical compositions comprising them.

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HETEROCYCLIC COMPOUNDS, PROCESSES FOR PRODUCING THEM AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

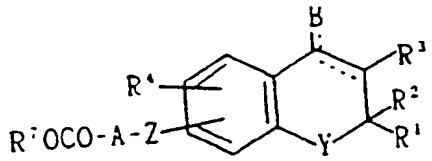
The present invention relates to novel heterocyclic compounds capable of inhibiting the biosynthesis of uric acid and also accelerating the excretion of said acid, to processes for producing them and to pharmaceutical compositions comprising them.

Hyperuricemia is a well known cause of gout, which is one of most popular diseses associated with hyperuricemia, and the number of patients suffering from gout is increasing. Hyperuricemia is also suggested to be a potential cause of certain angiopathys, such as ischemic cardiac disease and cerebrovascular disease. These diseases are associated with elevated levels of uric acid in plasma and urine, and have been treated with medicines which lower the uric acid level.

There are two kinds of medicines used for such treatments. One is a xanthine oxidase inhibitor which inhibits the biosynthesis of uric acid. The other is an eliminant which accelerates the excretion of uric acid. Examples of the inhibitor include Allopurinol and examples of the eliminant include Probenecid and Benzbromarone.

The present inventors have now discovered a class of heterocyclic compounds which can accelerate the excretion of uric acid and inhibit the biosynthesis of said acid through xanthine oxidase inhibition activity.

In particular, the present invention provides novel heterocyclic compounds of the formula (I):



(I)

wherein R^1 and R^2 are independently hydrogen, lower alkyl, phenyl or substituted phenyl, or R^1 and R^2 may form a four to eight-membered carbon ring together with the carbon atom to which they are attached, R^3 is hydrogen or lower alkyl; R^4 is one or two radicals selected from a group consisting of hydrogen, halogen, nitro, lower alkyl, phenyl, substituted phenyl, $-OR^5$ and $-SO_2NR^6R^7$, R^5 is hydrogen, lower alkyl, phenyl-substituted lower alkyl, carboxymethyl or ester thereof, hydroxyethyl or ether thereof, or allyl, R^6 and R^7 are independently hydrogen or lower alkyl, R^8 is hydrogen or a pharmaceutically active ester-forming group; A is a straight or branched hydrocarbon radical having one to five carbon atoms; B is halogen, oxygen, or dithiolane; Y is oxygen, sulfur, nitrogen or substituted nitrogen; Z is oxygen, nitrogen or substituted nitrogen, dotted line represents the presence or absence of a single bond

In other aspects the invention provides

(a) A pharmaceutical composition for the treatment or prophylaxis of hyperuricemia comprising a compound of the invention together with one or more pharmaceutically acceptable carriers diluents or excipients, said compositions preferably being in unit dosage form

(b) The use of a compound of the invention in the manufacture of a medicament for the treatment or prophylaxis of hyperuricemia.

As can be seen from the above formula (I), the compounds of the invention can be classified into three groups, derivatives of chromanone (where Y is oxygen) thiochromanone (where Y is sulfur), and 2,3,4-tetrahydroquinoline (where Y is nitrogen)

For the purpose of the present invention, as disclosed and claimed herein, the following terms are defined as below

The term "lower alkyl" refers to a straight or branched saturated hydrocarbon radical having one to five carbon atoms, including methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, and the like.

The term "lower alkoxy" refers to those formed from lower alkyls noted above, including methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy and the like.

The term "substituted phenyl" refers to phenyl substituted with halogen or lower alkyl, and the like. Examples of substituted phenyl include p-tolyl and p-chlorophenyl.

The term "four- to eight-membered carbon ring" refers to cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like.

The term "halogen atoms" refers to fluorine, chlorine, bromine, and iodine.

In the definition of R^5, the term "ester" used in the phrase "the ester of carboxymethyl" means a lower alkyl ester, such as methyl or ethyl ester; and the term "ether" used in the phrase "the ether of hydroxyethyl" means an ether which is formed by substitution of the hydrogen atom of the hydroxyl group in the hydroxyethyl group or aliphatic or aromatic alkyl group, such as benzyl.

In the definition of R^7, the phrase "pharmaceutically active ester-forming group" refers to a group which binds to a carboxyl group through an ester bond. Such ester-forming groups can be selected from carboxy-protecting groups commonly used for the preparation of pharmaceutically active substances, especially prodrugs. For the purpose of the invention, said group should be selected from those capable of binding to compounds of formula (I) wherein R^7 is hydrogen through an ester bond. Resultant esters are effective in increasing the stability, solubility, and absorption in the gastrointestinal tract of the corresponding non-esterified forms of said compounds (I), and also prolong the effective blood-level of it.

Additionally, the ester bond can be cleaved easily at the pH of body fluid or by enzymatic actions in vivo to provide a biologically active form of the compound (I). Preferred pharmaceutically active ester-forming groups include 1-(oxygen substituted)-C_2 to C_{15} alkyl groups, for example, a straight, branched, ringed, or partially ringed alkanoyloxyalkyl group, such as acetoxymethyl, acetoxyethyl, propionyloxymethyl, pivaloyloxymethyl, pivaloyloxyethyl, cyclohexaneacetoxyethyl, cyclohexanecarbonyloxycyclohexylmethyl, and the like, C_3 to C_{15} alkoxycarbonyloxyalkyl groups, such as ethoxycarbonyloxyethyl, isopropoxycarbonyloxyethyl, isopropoxycarbonyloxypropyl, t-butoxycarbonyloxyethyl, isopentyloxycarbonyloxypropyl, cyclohexyloxycarbonyloxyethyl, cyclohexylmethoxycarbonyloxyethyl, bornyloxycarbonyloxyisopropyl, and the like, C_2 to C_8 alkoxyalkyls, such as methoxy methyl, methoxy ethyl, and the like, C_4 to C_8 2-oxacycloalkyls such as, tetrahydropyranyl, tetrahydrofuranyl, and the like, substituted C_8 to C_{12} aralkyls, for example, phenacyl, phthalidyl, and the like, C_6 to C_{12} aryl, for example, phenyl xylyl, indanyl, and the like, C_2 to C_{12} alkenyl, for example, allyl, (2-oxo-1,3-dioxolyl)methyl and the like, and [4, 5-dihydro-4-oxo-1H-pyrazolo[3,4-d]pyrimidin-1-yl]methyl, and the like.

The carboxy-protecting groups may be substituted in various ways. Examples of substituents include halogen atom, alkyl, alkoxy, alkylthio and carboxy groups.

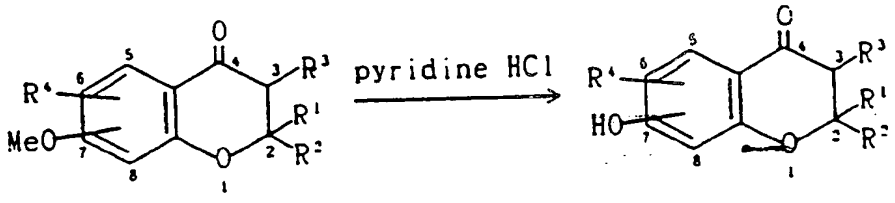
The term "straight or branched hydrocarbon radical" in the definition of A refers to methylene, ethylene, propylene, methylmethylene, or isopropylene. preferably from about 60 to about 80 °C. for about 30 minutes to about 10 hours, preferably about 1 to about 7 hours. Organic solvents which may be used are dry alcohols, such as dry methanol, ethanol, and the like.

Enamines which may be used in the reaction include compounds of formula (III) wherein R is 1-cyclohexene or 1-cyclopentene, or -C(Ph) = CH_2. A selected enamine is used in an approximately equimolar to slightly excess amount relative to the compound (II)

When the reaction is complete, the mixture is distilled to remove the solvent, and the residue is treated by column chromatography, preferably silica gel column chromatography, using an appropriate eluent for example, a mixture of ethyl acetate and hexane (1:2) or a mixture of ethyl acetate and dichloromethane (1:9 to 3:7) The eluate is concentrated to yield the compound(IV) as a thick syrup or a crude crystalline solid The latter can be purified by recrystallization from a solvent, for example, a mixture of diethyl ether and hexane, a mixture of benzene and hexane, or a mixture of ethyl acetate and hexane

The compound (IV) may be substituted with a lower alkyl group (-R^4) at the 3-position, if desired

Reaction Scheme 2



preferably from about 60 to about 80 °C. for about 30 minutes to about 10 hours, preferably about 1 to about 7 hours. Organic solvents which may be used are dry alcohols, such as dry methanol, ethanol, and the like.

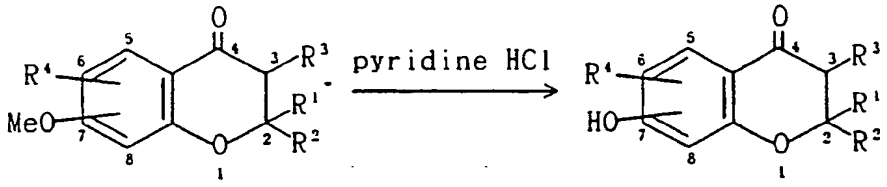
Enamines which may be used in the reaction include compounds of formula (III) wherein R is 1-

cyclohexene or 1-cyclopentene, or -C(Ph)=CH_2. A selected enamine is used in an approximately equimolar to slightly excess amount relative to the compound (II).

When the reaction is complete, the mixture is distilled to remove the solvent, and the residue is treated by column chromatography, preferably silica gel column chromatography, using an appropriate eluent, for example, a mixture of ethyl acetate and hexane (1:2) or a mixture of ethyl acetate and dichloromethane (1:9 to 3:7). The eluate is concentrated to yield the compound (IV) as a thick syrup or a crude crystalline solid. The latter can be purified by recrystallization from a solvent, for example, a mixture of diethyl ether and hexane, a mixture of benzene and hexane, or a mixture of ethyl acetate and hexane.

The compound (IV) may be substituted with a lower alkyl group (-R^3) at the 3-position, if desired.

Reaction Scheme 2



(IV) (V)

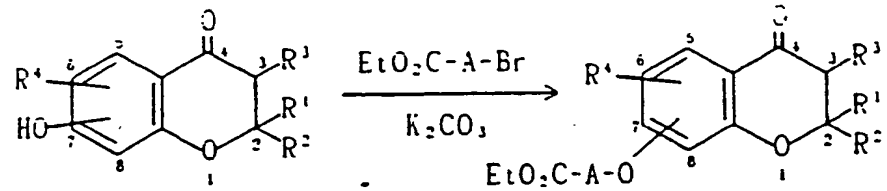
wherein R^1, R^2, R^3, and R^4 are as defined above.

In Reaction Scheme 2, the compound (IV) is reacted with pyridine hydrochloride to provide the compound (V).

The reaction is preferably conducted in dry pyridine hydrochloride at a temperature in the range of from about 150 to about 250 °C, preferably from about 200 to about 220 °C, for about 10 minutes to about 5 hours, preferably about 30 minutes to about one hour.

When the reaction is complete, water and diethyl ether are added to the reaction mixture, and the organic layer is separated. The organic solution is distilled to remove the ether. The residue is loaded on a silica gel column and eluted with an appropriate eluent, for example, a mixture of acetonitrile and dichloromethane (1:9 to 1:4), a mixture of ethyl acetate and dichloromethane (1:9), or diethyl ether. The eluate is concentrated to yield the compound (V) as a thick syrup or a crude crystalline solid. The latter can be purified by recrystallization from a solvent, such as a mixture of diethyl ether and hexane, diethyl ether, and the like.

Reaction Scheme 3



(V) (VI)

wherein R^1, R^2, R^3, R^4, and A are as defined above.

In Reaction Scheme 3, the compound (V) is reacted with an ethyl ester of a halogenated carboxylic acid of the formula: EtO_2C-A-Br in the presence of a base under nitrogen atmosphere.

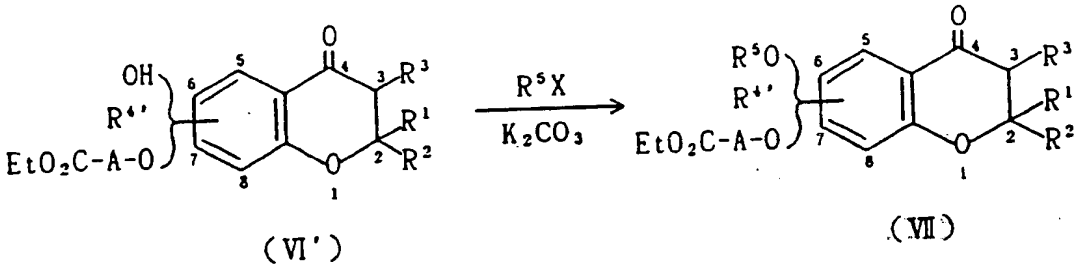
The reaction is preferably conducted in an organic solvent at a temperature in the range of from about 25 to about 100 °C, preferably from about room temperature to the boiling point of the solvent for about 1 to about 48 hours, preferably about 2 to about 20 hours.

Prefered organic solvents are polar solvents which include acetonitrile, dimethylformamide (DMF) and acetone, and is more preferably DMF. Bases which may be used include alkali or alkaline earth metal

carbonates. Prefered base is potassium carbonate. Ethyl esters of halogenated carboxylic acid which may be used include ethyl bromoacetate, ethyl bromopropionate, ethyl bromobutyrate, and the like. A selected ester is used in an approximately equimolar to slightly excess amount relative to the compound (V).

When the reaction is complete, the mixture is distilled to remove the solvent and the residue is extracted with diethyl ether. The ether extract is concentrated and the concentrate is subjected to recrystallization. Alternatively, the concentrate is treated by silica gel column chromatography using an appropriate eluent, such as dichloromethane, a mixture of ethyl acetate and dichloromethane (1:9), or a mixture of ethyl acetate and hexane (1:2). The eluate is concentrated to yield the compound (VI) as a crude crystalline solid, which is then recrystallized from a solvent, for example, cyclohexane, a mixture of diethyl ether and hexane or a mixture of benzene and hexane.

Reaction Scheme 4



(VI') (VII)

wherein R^1, R^2, R^3, and R^5, and A are as defined above. $R^{4'}$ is a radical selected from those listed in the definition of R^4 to the exclusion of a hydroxyl group, and X is halogen or -OTs.

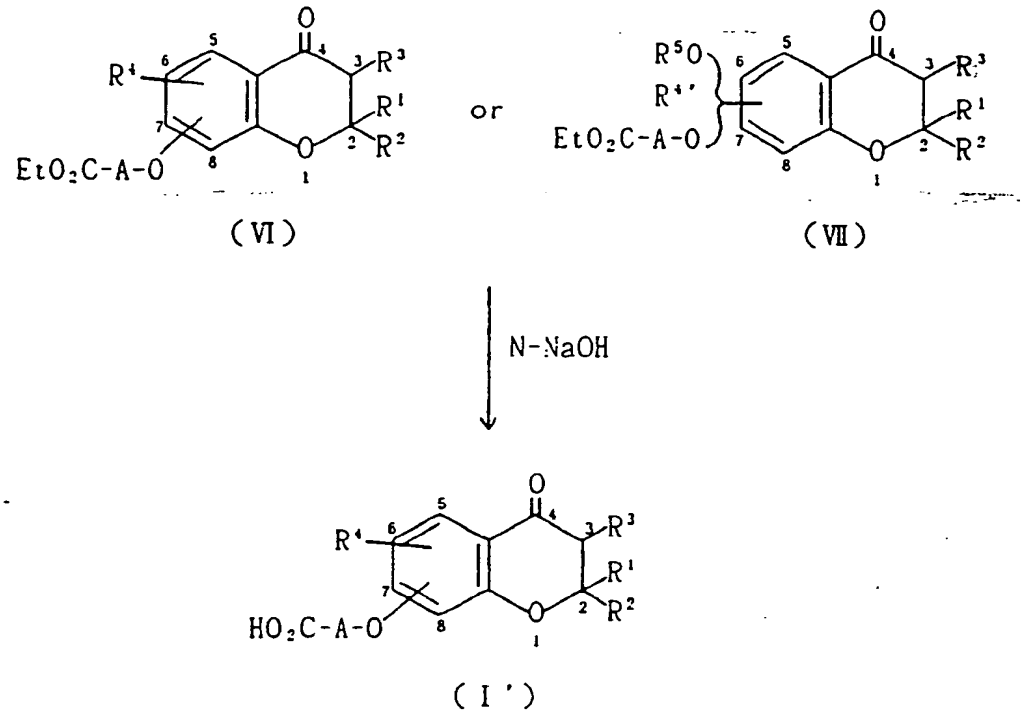
In Reaction Scheme 4, the compound (VI'), the same compound as the compound of formula (VI) wherein at least one of the substituents represented by R^4 is a hydroxyl group, is reacted with an alkylating agent (R^5X) in the presence of a base to provide the compound (VII).

The reaction is preferably conducted in an appropriate organic solvent such as DMF at a temperature in the range of from about 25 to about 100 °C, preferably from about room temperature to about 70 °C for about 1 to about 48 hours, preferably about 2 to about 20 hours.

Alkylating agents which may be used include methyl iodide, ethyl iodide, benzyl bromide, allyl bromide isopropyl iodide, $PhCH_2O(CH)_2OTs$, and the like. The base can be selected from those commonly used in the alkylation reaction with a preference of potassium carbonate. When the alkylating agent is $PhCH_2O(CH)_2OTs$, sodium hydride is employed.

When the reaction is complete, the mixture is distilled to remove the solvent and the residue is extracted with diethyl ether. The ether extract is concentrated, and the concentrate is treated by silica gel column chromatography. The compound (VII) is obtained as a thick syrup or a crude crystalline solid. Eluents which may be used are a mixture of ethyl acetate and dichloromethane (1:9), a mixture of acetone and dichloromethane (1:99 to 1:20), or a mixture of acetonitrile and dichloromethane (1:4). Solvents which may be used for the recrystallization are diethyl ether, a mixture of ethyl acetate and hexane, or a mixture of diethyl ether and hexane.

Reaction Scheme 5



(VI) (VII)

(I')

wherein R', R², R³, R⁴, R⁴', R⁵, and A are as defined above.

In Reaction Scheme 5, either of the compounds (VI) in Reaction Scheme 3 or the compound (VII) in Reaction Scheme 4 is treated with N-NaOH or trifluoroacetic acid to remove the carboxy-protecting group, whereby the compound (I') of the present invention is obtained.

The reaction is preferably conducted in an appropriate solvent, preferably ethanol at a temperature in the range of from about 10 °C to the boiling point of the solvent for about 10 minutes to about 48 hours preferably about 30 minutes to about 20 hours.

When the reaction is complete, the mixture is made acidic with hydrochloric acid and concentrated The residue is then recrystallized from an appropriate solvent, for example, diethyl ether, ethanol, ethylacetate acetone, a mixture of ethanol and water, a mixture of diethyl ether and hexane, a mixture of ethyl acetate and hexane, a mixture of acetone and hexane, or a mixture of acetone, ethyl acetate and diethyl ether

The resulting compound (I') in carboxylic acid form (R' in the formula (I) is hydrogen) can be converted easily into a pharmaceutically active ester to yield a prodrug as mentioned above Examples of pharmaceutically active esters are those formed with ester-forming groups listed above, including pivaloyloxymethyl phtalidyl, 1-hydroxymethylallopurinol, and the like Esterification can be carried out using standard procedures well known to those skilled in the art.

In the above description, only chromanone derivatives are illustrated However, one skilled in the art will readily appreciate that other classes of compounds of the formula (I), thiochromanones and quinolines, can be synthesized substantially in accordance with the Reaction Scheme illustrated above just by replacing the starting material (II) with a corresponding compound having a thioalcohol group (-SH) or amino group (-NH₂) instead of a hydroxyl group (-OH) in the formula (II).

The compounds of the formula (I) have been shown to accelerate the excretion of uric acid, and also inhibit the biosynthesis of uric acid through xanthine oxidase inhibitory activity as illustrated in the Experiments hereinafter described. Therefore, the compounds of the invention are useful for the treatment of various diseases associated with hyperuricemia, for example, gout, ischemic cardiac disease, and cerebrovascular disease.

The following Examples further illustrate the compounds of the present invention and methods for their synthesis. The Examples are not intended to be limiting to the scope of the invention in any respect and should not be so construed.

Preparation 1

(4′,6′-Dimethoxy-2′-hydroxy-3′-methylphenyl)ethanone

A mixture of 2,4,6-trimethoxytoluene (90% purity, 9.1 g, 45 mmol), acetyl chrolide (3.9 ml, 55 mmol), anhydrous aluminium chloride (7.98 g, 60 mmol), and anhydrous dichloromethane is stirred for 3 hours while cooling on ice.

The reaction mixture is then poured into ice-cooled water and the mixture is extracted with dichloromethane. The organic layer is separated and washed with water, dried, and concentrated to yield an oil. The oil is loaded onto a Lober column (Merck) and eluted with a mixture of acetyl chloride and dichloromethane (1:9)

From earlier fractions, the starting materials are recovered. From succeeding fractions, a crystalline solid is obtained (5.8 g, m.p. = 102 - 103 °C).

To a solution of the crystalline solid (5.2 g, 23 mmol) in dry dichloromethane (23 ml) is added dropwise a 2 M boron trichloride solution in dichloromethane (25 ml, 50 mmol) at -50 °C. The reaction mixture is stirred at -50 to -20 °C for 2 hours and then at -20 °C to room temperature for 2 hours. Ice-cooled water is added to the mixture and stirring is continued overnight at room temperature. The resulting mixture is extracted with dichloromethane, and the extract is washed with water, and concentrated to yield a crystalline residue. The residue is washed with diethyl ether to obtain the title compound as a crystalline solid (4.18 g, m.p. = 143 - 144 °C, yield 49.3%, based on the starting compound). Recrystallization from ethyl acetate gives a product having a melting point of 146 - 147 °C.

Elemental analysis (for $C_{11}H_{14}O_4$)		
Calcd.:	C, 62.85;	H, 6.71
Found:	C, 62.53;	H, 6.68

^{1}H-NMR ($CDCl_3$) δppm: 14.0(1H,s), 5.93(1H,s), 3.89(6H,s), 2.60(3H,s), 2.00(3H,s).
^{13}C-NMR ($CDCl_3$) δppm: 203.3, 163.8, 163.49, 105.73, 105.54, 85.6, 55.4, 55.3, 33.1, 7.1

Preparation 2

(2′-Chloro-6′-hydroxy-4′-methoxyphenyl)ethanone

To a solution of 3,5-dimethoxychlorobenzene (5.18 g, 30 mmol) and acetyl chloride (2.59 g, 33 mmol) in dry dichloromethane (30 ml) is added anhydrous aluminium chloride (4.4 g, 33 mmol) by portions at -15 to -10 °C and the mixture is stirred for 3 hours at the same temperature. The resulting reaction mixture is poured into ice-cold dilute hydrochloric acid, and the solution is extracted with dichloromethane. The organic layer is separated and washed with saturated brine, dried and concentrated. The residue is placed on a silica gel column and eluted with a mixture of hexane and ethyl acetate (2:1) to obtain an oil (5.25 g). To a solution of the oil (4.75 g, 20 mmol) in dry dichloromethane (22 ml) is added dropwise a 2M boron trichloride solution in dichloromethane (24.2 ml, 48.4 mmol), at -50 to -60 °C.

After stirring the mixture at -50 to -30 °C for 1 hour, ice-cold water is added thereto. The resulting mixture is extracted with dichloromethane, and the organic layer is washed with saturated brine, dried and concentrated. A crystalline residue is recrystallized from hexane to obtain the title compound (3.91 g, yield 72.1%, based on the starting compounds, m.p. = 54 to 55 °C).

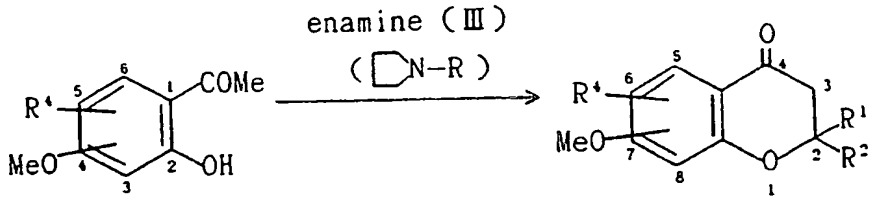
^{1}H-NMR ($CDCl_3$) δppm: 13.47(1H,s), 6.55(1H, d, J = 2.6), 6.37(1H,d, J = 2.6), 3.83(3H,s), 2.81(3H,s).

Preparation 3

6-Methoxyspiro[2H-1-benzopyran-2,1′-cyclohexan]-4(3H)-one

A solution of (2′-hydroxy-5′methoxyphenyl)ethanone (3.32 g, 20 mmol) and cyclohexanonepyrrolidine (enamine form) (3.18 g, 21 mmol) in dry ethanol (40 ml) is heated to reflux for 1.5 hours under nitrogen gas. The solvent is removed by distillation, and the residue is dissolved in diethyl ether, washed with dilute HCl and then water, dried, and concentrated. The residue is placed on a silica gel column and eluted with a mixture of ethyl acetate and hexane (1:2) to obtain the title compound as thick syrup (4.5 g, yield 91.3%).

Preparations 4 - 11



(Ⅱ) (Ⅳ)

In Preparations 4 - 11, corresponding compounds (IV) were prepared according to the procedure of Preparation 3 employing the starting materials (II) and reaction conditions shown in Table 1. Physicochemical properties of each product are given in Table 2. The term "starting material" refers to the compound used in the reaction. Said compound is depicted by the number of Preparation or literature which gives or discloses the same.

Table 1

Compd. of Prep. No.	(II) material	(II) position of -OMe	(II) R⁴	(II) mmol	(III) R	(III) mmol	MeOH (ml)	Reaction conditions Time (hr)	Reaction conditions Column chromato Eluent	(IV) R¹	(IV) R²	(IV) R⁴	(IV) position of -OMe	Yield (%)
3	a)	5	H	20	1-cyclohexene	21	40	1.5	ethyl acetate-hexane 1:2	-$(CH_2)_3$-		H	6	91
4	b)	4	H	10	1-cyclohexene	11	25	1	ethyl acetate-dichloro methane 1:9	-$(CH_2)_3$-		H	7	87
5	c)	4	3-OMe	20	1-cyclohexene	22	40	1	---	-$(CH_2)_3$-		8-OMe	7	61
6	d)	4	6-OMe	10	-C(Ph)$-CH_3$	12	30	7	ethyl acetate-dichloro methane 1:9 - 3:7	Me	Ph	5-OMe	7	20
7	d)	4	6-OMe	10	1-cyclopentene	10	30	1	ethyl acetate-dichloro methane 1:9	-$(CH_2)_4$-		5-OMe	7	76
8	d)	4	6-OMe	10	1-cyclohexene	12	25	0.7	ethyl acetate-dichloro methane 1:9	-$(CH_2)_3$-		5-OMe	7	92
9	e)	4	6-Me	10	1-cyclohexene	11	25	1	ethyl acetate-dichloro methane 1:9	-$(CH_2)_3$-		5-Me	7	60
10	f)	4	6-OMe 3-Me	10	1-cyclohexene	11	25	1	ethyl acetate-dichloro methane 1:9	-$(CH_2)_3$-		5-OMe 8-Me	7	76
11	g)	4	6-CO	19	1-cyclohexene	21	48	1.5	ethyl acetate-hexane 1:2	-$(CH_2)_3$-		5-CO	7	56

a) St. v. Kostanecki and V. Lampe, Chem. Ber., 37, 773(1904)

b) Y. Tahara, Chem. Ber., 24, 2459(1891)

c) E. David and St. v. Kostanecki, Chem. Ber., 36, 125(1903)

d) St. v. Kostanecki and J. Tambor, Chem. Ber., 32, 226(1899)

e) J. Tambor, Chem. Ber., 41, 793(1908)

f) Preparation 1

g) Preparation 2

Table 2

Compd. of Prep. No.	M.p. (recrystallized)	Molecular formula	Elemental analysis			^{1}H-NMR(CDCl$_3$) δ ppm(J Hz)
			C	H	Cl	
3	thick syrup					7.30(1H,d,J = 2.5), 7.10(1H,dd,J = 9.0 and 2.5), 6.86(1H,d,J = 9.0), 3.78(3H,s), 2.66(2H,s), 2.1-1.3(10H,m)
4	thick syrup					7.78(1H,d,J = 9.0), 6.50(1H,dd,J = 9.0 and 2.0), 6.40(1H,d,J = 2.0), 3.82(3H,s), 2.63(2H,s), 2.2-1.2(10H,m)
5	78-79 ether-hexane					7.64(1H,d,J = 9.0), 6.10(1H,d,J = 9.0), 3.92(6H,s), 6.77(2H,s), 2.3-1.2(10H,m)
6	137-138 benzene-hexane	$C_{18}H_{18}O_4$	72.47 (72.51)	6.13 (6.28)		7.5-7.1(5H,s), 6.19(1H,d,J = 2.0), 5.97(1H,d,J = 2.0), 3.81(3H,s), 3.78(3H,s), 3.20(1H,d,J = 16.5), 2.95(1H,d,J = 16.5), 1.70(3H,s)
7	thick syrup					6.03(2H,s), 3.88(3H,s), 3.82(3H,s), 2.73(2H,s), 2.2-1.4(8H,m)
8	115-116 ether-hexane	$C_{16}H_{20}O_4$	69.54 (69.55)	7.30 (7.23)		6.07(1H,d,J = 2.0), 6.00(1H,d,J = 2.0), 3.85(3H,s), 3.80(3H,s), 2.61(2H,s), 2.0-1.3(10H,m)
9	thick syrup					6.30(2H,s), 3.80(3H,s), 2.61(s) and 2.58(s)(5H), 2.2-1.2(10H,m)
10	174-175 ether-hexane					6.09(1H,s), 3.90(6H,s), 2.60(2H,s), 2.05-1.2(13H,m)
11	83-84 ethyl acetate-hexane	$C_{15}H_{17}ClO_5$	64.17 (63.92)	6.10 (6.15)	12.63 (12.52)	6.57(1H,d,J = 2.4), 6.78(1H,d,J = 2.4), 3.83(3H,s) 2.68(2H,s), 2.0-1.25(10H,m)

Preparation 12

5,6-Dichloro-7-methoxyspiro[2H -1-benzopyran-2,1'-cyclohexan]-4(3H)-one (12-1) and 5,8-dichloro-7-methoxyspiro[2H -1-benzopyran-2,1'-cyclohexan]-4(3H)-one (12-2)

To a solution of 5-chloro-7-methoxyspiro[2H -1-benzopyran-2,1'-cyclohexan]-4(3H)-one (prepared in Preparation 11) (0.63 g, 2.25 mmol) in dry dichloromethane (10 ml) is added dropwise a solution of sulfuryl chloride (0.345 g, 2.56 mmol) in dichloromethane (4.5 ml) at -35 to -30 °C over 10 minutes. The mixture is then continuously stirred at a temperature ranging from -30 to -20 °C for half an hour, at 0 to 3 °C for one hour, and 3 °C to room temperature for half an hour. The solvent is removed and the residue is treated with diethyl ether. The mixture is filtered to obtain the crystalline compound (compound No. 12-1) (0.375 g, yield

53%, m.p. = 167 - 168 °C).

The filtrate is concentrated and the residue is diluted with hexane. The resulting precipitate is collected by filtration to yield a mixture of crystalline compound (12-1) and compound (12-2) (0.22 g, m.p. = 109 - 112 °C, (12-1):(12-2) = 1:3). Recrystallization from ethyl acetate gives a pure compound (12-2) having a melting point of 126 to 127 °C.

Compound (12-1)

Elemental analysis (for $C_{15}H_{16}Cl_2O_3$)			
Calcd.:	C, 57.16;	H, 5.12;	Cl, 22.49
Found:	C, 57.16;	H, 5.09;	Cl, 22.53

^{1}H-NMR ($CDCl_3$) δppm: 6.47(1H,s), 3.95(3H,s), 2.70(2H,s), 2.0 - 1.25(10H,m).

^{13}C-NMR ($CDCl_3$) δppm: 188.69, 160.63, 160.27, 133.22, 117.03, 112.35, 99.87, 80.46, 56.7, 48.82, 34.60, 25.06, 21.46

Compound (12-2)

Elemental analysis (for $C_{15}H_{16}Cl_2O_3$)			
Calcd.:	C, 57.16;	H, 5.12;	Cl, 22.49
Found:	C, 57.26;	H, 5.08;	Cl, 22.50

^{1}H-NMR ($CDCl_3$) δppm: 6.65(1H,s), 3.97(3H,s), 2.70(2H,s), 2.2 - 1.1(10H,m) ^{13}C-NMR ($CDCl_3$) δppm 189.2, 159.4, 157.32, 133.48, 112.97, 109.87, 107.97, 81.25, 56.68, 49.30, 34.71, 25.15, 21.37

Preparation 13

5,7-Dimethoxy-3-methylspiro[2H-1-benzopyran-2,1'-cyclohexan]-4(3H)-one

A solution of 5,7-dimethoxyspiro[2H-1-benzopyran-2,1-cyclohexan]-4(3H)-one (prepared in Preparation 8) (1.38 g, 5 mmol) in dry tetrahydrofuran (10 ml) is added dropwise at -78 °C to a solution of lithium diisopropylamide (prepared from diisopropylamine (0.77 ml, 7.6 mmol) and 1.3N butyl lithium solution in hexane (3.85 ml, 5.0 mmol)) in tetrahydrofuran. To the mixture is added hexamethyl phosphoric triamide (1.05 ml) and then a solution of methyl iodide (0.78 g, 5.5 mmol) in tetrahydrofuran (1 ml) at -70 °C. After the mixture is reacted at -78 to 0 °C for 2.5 hours and then at 0 to 3 °C for 2 hours, an aqueous solution of ammonium chloride is added thereto. The mixture is then extracted with diethyl ether and the organic layer is separated, washed twice with saturated brine, dried and the solvent is removed by distillation. The residue is loaded onto a Lober column and eluted with a mixture of acetonitrile and dichloromethane (1:9) to obtain the title compound as an oil (1.01 g, yield 69.6%).

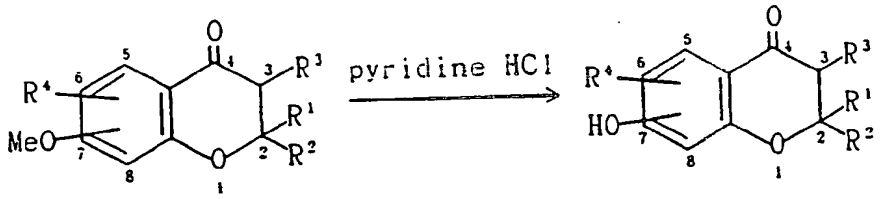
^{1}H-NMR ($CDCl_3$) δppm: 6.08(1H,d,J = 2), 6.02(1H,d,J = 2), 3.87(3H,s), 3.83(3H,s), 2.51(1H,q,J = 7), 2.1 - 1.3(10H,m), 1.13(3H,d,J = 7).

Preparation 14

6-Hydroxyspiro[2H-1-benzopyran-2,1'-cyclohexan]-4(3H)-one

A mixture of 6-methoxyspiro[2H -1-benzopyran-2,1′-cyclohexan]-4(3H)-one (prepared in Preparation 3) (1.0 g, 4.06 mmol) in dry pyridine HCl (6 g, 52 mmol) is heated to 210 - 215 °C on an oil bath for 45 minutes with stirring, and allowed to cool. The mixture is extracted with water and diethyl ether. The ether layer is separated, washed with dilute hydrochrolic acid and then water, dried and concentrated. The residue is placed on a silica gel column and eluted with a mixture of acetonitrile and dichloromethane (1:9 to 1:4) to obtain the title compound as an oil (0.81 g, yield 85.5%).

Preparation 15 - 25



(Ⅳ) (Ⅴ)

In Preparations 15 to 25, corresponding compounds (V) are prepared subatantially in accordance with procedures described in Preparation 14 using starting materials (IV) and reaction conditions shown in Table 3. Physicochemical properties of each product are given in Table 4.

Table 3

Compd. of Prep. No.	(IV)			reaction conditions			(V)					
	material	mmol	pyridine HCl (mmol)	Temp (°C)	Time (hr)	Chromato Eluent	R^1	R^2	R^3	R^4	position of -OMe	Yield (%)
14	3	4 06	52	210-215	0 8	acetonitrile-dichloromethane 1:9-1:4	$-(CH_2)_5-$		H	H	6	86
15	4	7 0	100	210-220	1	ethyl acetate-dichloro methane 1:9	$-(CH_2)_5-$		H	H	7	92
16	5	10 87	156	210-215	1	---	$-(CH_2)_5-$		H	8-OH	7	81
17	6	3 1	31	200-215	0 7	ether	Me • Ph		H	5-OH	7	78
18	7	7 62	103	210-220	1	ethyl acetate-dichloro methane 1:9	$-(CH_2)_4-$		H	5-OH	7	80
19	8	10 7	110	210-220	1	ether	$-(CH_2)_5-$		H	5-OH	7	97
20	9	6 0	81	210-220	1	ethyl acetate-dichloro methane 1:9	$-(CH_2)_5-$		H	5-Me	7	71
21	10	6 0	81	210-220	1	ethyl acetate-dichloro methane 1:9	$-(CH_2)_5-$		H	5-OH 8-Me	7	76
22	11	5 34	65	210-215	1	ethyl acetate-dichloro methane 1:9	$-(CH_2)_5-$		H	5-Cl	7	67
23	12-1	1 59	43	210	0 5	ethyl acetate-dichloro methane 1:9	$-(CH_2)_5-$		H	5-Cl 6-Cl	7	79
24	12-2	2 6	35	205-215	0.5	---	$-(CH_2)_5-$		H	5-Cl 8-Cl	7	49
25	13	7 6	103	210-220	1	ethyl acetate-dichloro methane 1:9	$-(CH_2)_5-$		Me	5-OH	7	96

Table 4

Compd. of Prep. No.	M.p. (°C) (recrystallized)	Molecular formula	Elemental analysis(found)			^{1}H-NMR($CDCl_3$) δ ppm(J Hz)
			C	H	Cl	
14	thick syrup					7.40(1H,d,J = 2.5), 7.10(1H,dd,J = 9.0 and 2.5), 6.85(1H,d,J = 9.0), 6.85(1H,b), 2.68(2H,s), 2.1-1.2(10H,m)
15	171-172					7.90(1H,s), 7.79(1H,d,J = 9.0), 6.54(1H,dd,J = 9.0 and 2.0), 6.44(1H,d,J = 2.0), 2.68(2H,s), 2.2-1.2(10H,m)
16	83-84 ether-hexane	$C_{14}H_{10}O_4$	67.73 (67.60)	6.50 (6.82)		7.43(1H,d,J = 9.0), 6.73(1H,s), 6.60(1H,d,J = 9.0), 5.83(1H,s), 2.71(2H,s), 2.2-1.3(10H,m)
17	thick syrup					7.5-7.2(5H,m), 6.05(1H,d,J = 2.0), 5.88(1H,d,J = 2.0) 3.30(1H,d,J = 16.5), 3.03(1H,d,J = 16.5), 1.70(3H,s)
18	thick syrup					11.97(1H,s), 7.50(1H,bs), 5.96(1H,d,J = 2.0), 5.89(1H,d,J = 2.0), 2.78(2H,s), 2.2-1.5(8H,m)
19	140-141 ether	$C_{14}H_{18}O_4$	67.73 (67.73)	6.50 (6.52)		11.97(1H,s), 7.68(1H,s), 5.95(2H,s), 2.65(2H,s), 2.1-1.2(10H,m)
20	171-172					7 57(1H,s), 6.34(2H,s), 2 66(s) and 2 60(s)(5H), 2 1-1 3(10H m) in acetone-d_6 6 00(1H,s) 3 1(2H,b), 2.65(2H,s), 2 0(3H s) 2 2-1 1(10H,m)
21	179-180					
22	188-189 ether-hexane	$C_{14}H_{15}ClO_3$	63.04 (63.02)	5.67 (5 70)	13.29 (13.10)	6 84(1H,s), 6 58(1H,d,J = 2 4) 6.39(1H,d,J = 2 4), 2 7(2H,s), 2 0-1.25(10H,m)
23	189-191	$C_{14}H_{14}Cl_2O_3$	55.83 (55.73)	4.69 (4.74)	23.54 (23.53)	6.60(1H,s), 6.23(1H,b), 2.68(2H,s), 2.05-1.15(10H,m)
24	thick syrup					6.78(1H,s), 6.60(1H,bs), 2.72(2H,s), 1.2-1.1(10H,m)
25	thick syrup					12.0(1H,s), 7.3(1H,bs), 5.95(2H,bs), 2.54(1H,q,J = 7.0), 2.1-1.1(10H,m), 1.19(3H,d,J = 7.0)

Preparation 26

5,7-dihydroxyspiro[2H -1-benzopyran-2,1′-cyclohexan]-4(3H)-one

A mixture of 5,7-dimethoxyspiro[2H -1-benzopyran-2,1′-cyclohexan]-4(3H)-one [H.F.Birch, A. Robertson, and T.S.Subramanjam, J.Chem.Soc., 1832 (1936)] (1.3 g, 6.25 mmol) and 48% hydrobromic acid (50 ml) is heated to reflux for one hour. After cooling, the reaction mixture is concentrated under reduced pressure. The concentrate is extracted with diethyl ether and the extract is washed with water, dried, and concentrated. The residue is placed on a silica gel column and eluted with diethyl ether. The eluate is treated with ether to yield the title compound as a crystalline solid (0.65 g, 58%).

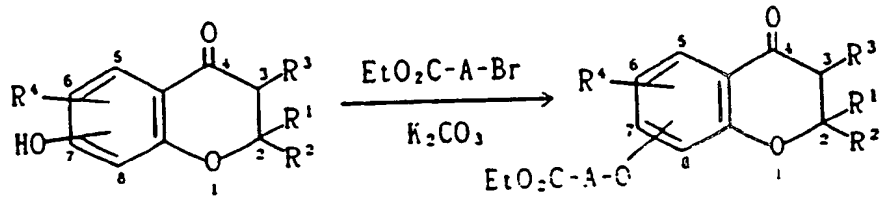
^{1}H-NMR (d_6-acetone) δppm: 5.92(2H,s), 4.46(2H,t,J=6.5), 3.16(2H,s), 2.75(2H,t,J=6.5).

Preparation 27

Ethyl [(3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-6-yl)oxy]acetate

A mixture of 6-hydroxy-spiro[2H -1-benzopyran-2,1′-cyclohexan]-4(3H)-one (prepared in Preparation 14) (0.878 g, 3.78 mmol), ethyl bromoacetate (0.69 g, 4.13 mmol), anhydrous potassium carbonate (0.78 g, 5.65 mmol) and dry N , N -dimethylformamide (DMF) (7.5 ml) is stirred at room temperature for 4 hours under nitrogen gas. DMF is removed by distillation under reduced pressure and the residue is extracted with diethyl ether. The ether layer is separated and washed successively with water, dilute sodium hydroxide and saturated brine, dried and distilled to remove ether. The residue is recrystallized from cyclohexane to obtain the title compound as a crystalline solid (1.11 g, yield 92.5%, m.p. = 72-73 °C)

Preparation 28 - 44



(V) (VI)

In Preparations 28 to 44, corresponding compounds (VI) were prepared according to the procedure of Preparation 27 employing the starting materials (V) and reaction conditions given in Table 5. Purification was conducted by means of silica gel column chromatography. Physicochemical properties of each product are shown in Table 6.

Table 5

Compd. of Prep. No.	V material	V mmol	Ethyl bromoacetate (mmol)	Potassium carbonate (mmol)	CH_3CN (ml)	Reaction conditions Temp. (°C)	time (hrs.)	Chromato Eluent	VI R^1	R^2	R^3	R^4	position of $-OCH_2COOEt$	Yield (%)
27	14	3.78	4.13	5.65	7.5	25	4	---	$-(CH_2)_5-$		H	H	6	93
28	15	6.0	6.0	9.0	18	25	4	ethyl acetate-dichloromethane 1:9	$-(CH_2)_5-$		H	H	7	98
29	17	2.7	2.7	4.1	8	25	20	ethyl acetate-dichloromethane 1:9	Me	Ph	H	5-OH	7	84
30	18	6.0	6.0	9.0	18	25	4	ethyl acetate-dichloromethane 1:9	$-(CH_2)_4-$		H	5-OH	7	79
31	19	9.03	9.03	15	27	25	20	ethyl acetate-dichloromethane 1:9	$-(CH_2)_5-$		H	5-OH	7	86
32	19	4.03	9.3	10	15 (DMF)	25	2.5	dichloromethane	$-(CH_2)_5-$		H	5-OCH_2COOEt	7	91
33	25	6.0	6.0	9.0	18	25	4	ethyl acetate-dichloromethane 1:9	$-(CH_2)_5-$		H	5-OH	7	87
34	20	6.0	6.0	9.0	18	25	4	ethyl acetate-dichloromethane 1:9	$-(CH_2)_5-$		H	5-Me	7	96
35	21	6.0	6.0	9.0	18	25	4	ethyl acetate-dichloromethane 1:9	$-(CH_2)_5-$		H	5-OH 8-Me	7	91
36	22	3.52	3.87	5.3	9 (acetone)	reflux	2	ethyl acetate-hexane 1:2	$-(CH_2)_5-$		H	5-Cl	7	82

Table 5 (continued)

Compd. of Prep. No.	V material	V mmol	Ethyl bromoacetate (mmol)	Potassium carbonate (mmol)	CH_3CN (mℓ)	Reaction conditions Temp. (℃)	Time (hrs.)	Chromato Eluent	VI R^1	R^2	R^3	R^4	position of $-OCH_2COOEt$	Yield (%)
37	23	1.26	1.5	1.9	6	25	20	ethyl acetate-hexane 1:2	$-(CH_2)_5-$		H	5-Cℓ 6-Cℓ	7	90
38	24	1.26	1.5	1.9	6	25	20	ethyl acetate-hexane 1:3	$-(CH_2)_5-$		H	5-Cℓ 8-Cℓ	7	63
39	26	4.66	4.66	7.0	14	25	16	---	H	H	H	5-OH	7	80
40	a)	6.64	6.97	10	20	25	20	---	H	H	H	H	7	100
41	b)	7.0	7.32	10.5	20	25	20	---	Me	Me	H	H	7	98
42	c)	7.0	7.32	10.5	20	25	20	---	H	Me	H	H	7	93
43[1]	d)	2.51	2.76[a]	5.0	5	25	3	ethyl acetate-dichloromethane 1:9	H	Ph	H	H	7	85
44	e)	11.53	11.64	17.39	34	25	16	ethyl acetate-dichloromethane 1:9	Me	Me	H	5-OH	7	88

a) P. Naylor, G. R. Ramage and F. Schofield, J. Chem. Soc., 1190 (1958).
R^1, R^2, R^3, R^4: H, position of -OH: 7-position

b) J. Arima, J. Chem Soc. Japan, 53, 715(1932).
D. Sowmithran, and K J R Prasad, Synthesis, 545 (1985).
R^1, R^2: Me
R^3, R^4: H, position of-OH: 7-position

c) M. Miyano and M Matsui, Bull. Chem Soc Japan, 31, 397(1958).
R^1, R^3, R^4: H, position of-OH: 7-position
R^2: Me

Table 5 (continued)

d) Y. Tatsuta, J.Chem.Soc., Japan, 61, 752 (1940).
R^1, R^3, R^4: H, position of-OH: 7-position
R^2: Ph

e) F. Camps, J. Coll, A. Messegner, M. A. Pericas, S. Ricart, W. S. Bowers and D. M. Soderland, Synthesis, 725 (1980).
R^1, R^2: Me
R^3: H
R^4: 5-OH, position of-OH: 7-position

f) t-Butyl ester

g) t-Butyl bromoacetate

Table 6

Compd. of Prep. No.	M.p. °C (recrystallized)	Molecular formula	Elemental analysis (found) C	H	^{1}H-NMR CDCl$_3$ δ ppm (J Hz)
27	72-73 cyclohexane	$C_{16}H_{22}O_5$	67.91 (67.85)	6.96 (7.07)	7.23-7.10(2H, m), 6.90(1H, d, J = 9.0), 4.58(2H, s), 4.26(2H, q, J = 7.0). 2.65(2H, s), 2.1-1.2(13H, m)
28	66 cyclohexane	$C_{16}H_{22}O_5$	67.91 (67.70)	6.96 (7.14)	7.81(1H, d, J = 9.0), 6.56(1H, dd, J = 9.0 and 2.5), 6.40(1H, d, J = 2.5). 4.66(2H, s), 4.28(2H, q, J = 7.0), 2.67(2H, s), 2.2-1.2(10H, m), 1.31(3H, t, J = 7.0)
29	138.5 139 5 benzene-hexane	$C_{20}H_{20}O_6$	67.40 (67.50)	5.66 (5.73)	11.8(1H, s), 7.5-7.2(5H, m), 6.1(1H, d, J = 2.2), 5.90(1H, d, J = 2.2). 4.60(2H, s), 4.25(2H, q, J = 7.0), 3.26(1H, d, J = 16.5), 3.00(1H, d, J = 16.5). 1.70(3H, s), 1.26(3H, t, J = 7.0)
30	thick syrup				12.0(1H, s), 5.95(2H, s), 4.61(2H, s), 4.29(2H, q, J = 6.0), 2.79(2H, s). 2.3 1.5(8H, m), 1.30(3H, t, J = 6.0)
31	70-71				11 98(1H, s), 5.98(2H, s), 4.61(2H, s), 4.27(2H, q, J = 7.0), 2.65(2H, s). 2.1-1.2(13H, m)
32	87 88 ethyl acetate-hexane	$C_{21}H_{20}O_6$	62.85 (62.77)	6.71 (6.78)	6.00(1H, d, J = 2.4), 5.97(1H, d, J = 2.4), 4.61(2H, s), 4.57(2H, s). 4.35-4.15(4H, m), 2.61(2H, s), 2.0-1.4(10H, m), 1.28(6H, t, J = 7.2)
33	thick syrup				11 93(1H, s), 5.98(2H, bs), 4.60(2H, s), 4.27(2H, q, J = 7.0). 2.57(1H, q, J = 7.0), 2.1-1.1(10H, m), 1.29(3H, t, J = 7.0), 1.17(3H, d, J = 7.0)
34	thick syrup				6.36(1H, d, J = 2.5), 6.27(1H, d, J = 2.5), 4.63(2H, s), 4.39(2H, q, J = 6.0). 2.66(s) and 2.60(s)(5H), 2.1-1.2(10H, m), 1.29(3H, t, J = 6.0)
35	102-103 ether-hexane	$C_{18}H_{24}O_6$	65.50 (65.57)	6.94 (7.06)	12 0(1H, s), 5.85(1H, s), 4.63(2H, s), 4.26(2H, q, J = 7.0), 2.63(2H, s). 2.09(3H, s), 2.0-1.2(13H, m)
36	thick syrup				6.60(1H, d, J = 2.7), 6.35(1H, d, J = 2.7), 4.61(2H, s), 4.28(2H, q, J = 7.0). 2.67(2H, s), 2.1-1.2(10H, m), 1.28(3H, t, J = 7.0)
37	126-127				6.31(1H, s), 4.75(2H, s), 4.31(2H, q, J = 7.0), 2.71(2H, s), 2.0-1.3(13H, m)
38	thick syrup				6.[illegible](1H, s), 4.75(2H, s), 4.30(2H, q, J = 7.0), 2.71(2H, s), 2.2-1.2(13H, m)

Table 6 (continued)

Compd. of Prep. No.	M. p. °C (recrystallized)	Molecular formula	Elemental analysis (found) C	H	^{1}H-NMR CDCℓ$_3$, δ ppm(J Hz)
39	121-122 benzene-hexane	$C_{13}H_{14}O_6$	58.64 (58.52)	5.30 (5.35)	12.0(1H, s), 5.98(2H, s), 4.58(2H, s), 4.44(2H, t, J=6.5), 4.25(2H, q, J=7), 2.75(2H, t, J=6.5), 1.28(3H, t, J=7)
40	71-72 ether-hexane	$C_{13}H_{14}O_5$	62.39 (62.25)	5.64 (5.84)	7.87(1H, d, J=9.0), 6.63(1H, dd, J=9.0 and 2.5), 6.41(1H, d, J=2.5), 4.66(2H, s), 4.53(2H, t, J=6.0), 4.30(2H, q, J=7.0), 2.76(2H, t, J=6.0), 1.30(3H, t, J=7.0)
41	88-89 ether-hexane	$C_{15}H_{18}O_5$			7.83(1H, d, J=9.0), 6.58(1H, dd, J=9.0 and 2.5), 6.36(1H, d, J=2.5), 4.64(2H, s), 4.28(2H, q, J=7.0), 2.67(2H, s), 1.44(6H, s), 1.30(3H, t, J=7.0)
42	78-79 ether-hexane	$C_{14}H_{16}O_5$	63.63 (63.58)	6.10 (6.32)	7.85(1H, d, J=9.0), 6.60(1H, dd, J=9.0 and 2.5), 6.40(1H, d, J=2.5), 4.66(2H, s), 4.58(1H, m), 4.28(2H, q, J=7.0), 2.63(2H, d, J=8.0), 1.43(3H, d, J=6.0), 1.30(3H, t, J=7.0)
43	thick syrup				7.87(1H, d, J=9.0), 7.43(5H, bs), 6.63(1H, dd, J=9.0 and 2.0), 6.45(1H, d, J=2.0), 5.45(1H, dd, J=12.0 and 4.5), 4.52(2H, s), 3.55(1H, dd, J=16.5 and 12.0), 2.70(1H, dd, J=16.5 and 4.5), 1.48(9H, s)
44	61-62 ether-hexane	$C_{15}H_{18}O_6$	61.22 (61.15)	6.17 (6.14)	12.0(1H, s), 5.95(2H, s), 4.62(2H, s), 4.28(2H, q, J=7.0), 2.70(2H, s), 1.47(6H, s), 1.32(3H, J=7.0)

Preparation 45

Diethyl {(3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7,8-yl)dioxy}diacetate (45-1), Methyl {(7-hydroxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-8-yl)oxy}acetate (45-2), and Methyl {(8-hydroxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}acetate (45-3)

A mixture of 7,8-dihydroxyspiro[2H -1-benzopyran-2,1′-cyclohexan]-4-(3H)one (prepared in Preparation 16) (4.02 g, 16.2 mmol), ethyl bromoacetate (2.98 g, 17.8 mmol), anhydrous potassium carbonate (3.35 g, 24.3 mmol), and dry acetonitrile (49 ml) is stirred overnight at room temperature. The mixture is filtered to remove the inorganic substance and the filtrate is distilled. To the residue is added diethyl ether and the mixture is extracted with 1N sodium hydroxide. The ether layer is separated, washed with water, dried, and concentrated to yield the title compound (45-1) as a syrup (2.0 g, yield 29%). The aqueous layer is made acidic with dilute hydrochloric acid and extracted with diethyl ether. The ether layer is separated and extracted with aqueous sodium bicarbonate. The aqueous layer is made acidic with dilute hydrochloric acid and extracted with ether. The extract is washed with water, dried and concentrated. To the concentrate is added a mixture of diazomethane and ether to form methyl ester. The mixture is distilled to give a residue (1.8 g) containing the title compounds (45-2) and (45-3). The residue is placed onto a Lober column and eluted with a mixture of ethyl acetate and dichloromethane (1:9). From the earlier fractions, the compound (45-2) is obtained as a crystalline solid (0.4 g, 7.4%, m.p. = 118 - 119 °C). From the succeeding fractions, the another compound (45-3) is obtained as a syrup (0.6 g, yield 11.5%)

Compound (45-1)

^{1}H-NMR ($CDCl_3$) δppm: 7.58(1H,d,J = 9), 6.47(1H,d,J = 9), 4.76(2H,s), 4.73(2H,s), 4.30(2H,q,J = 7), 4.23-(2H,q,J = 7), 2.66(2H,s), 2.2 - 1.2(16H,m)

Compound (45-2)

^{1}H-NMR ($CDCl_3$) δppm: 8.53(1H,s), 7.57(1H,d,J = 9), 6.56(1H,d,J = 9), 4.71(2H,s), 3.83(3H,s), 2.65(2H,s), 2.15 - 1.2(10H,m)

Compound (45-3)

^{1}H-NMR ($CDCl_3$) δppm: 7.40(1H,d,J = 9), 6.50(1H,d,J = 9), 6.27(1H,s), 4.76(2H,s), 3.82(3H,s), 2.70(2H,s), 2.1 - 1.2(10H,m)

Preparation 46

Ethyl 2-{(5-hydroxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-6-yl)oxy}propionate

A mixture of 5,7-dihydroxyspiro[2H -1-benzopyran-2,1′-cyclohexan]-4(3H)-one (prepared in Preparation 19) (0.248 g, 1.0 mmol), ethyl 2-bromopropionate (0.199 g, 1.1 mmol), anhydrous potassium carbonate (0.207 g, 1.5 mmol), and acetonitrile (3 ml) is stirred at room temperature for 22 hours, and the reaction mixture is concentrated. To the residue is added saturated brine and the mixture is extracted with dichloromethane. The organic layer is separated, dried, and concentrated. Purification by silica gel column chromatography (eluent: dichloromethane) gives the title compound as an oil (0.284 g, yield 81.6%).

^{1}H-NMR ($CDCl_3$) δppm: 11.94(1H,s), 5.93(2H,s), 4.73(1H,q, J = 6.8), 4.21(2H,q,J = 7), 2.63(2H,s), 1.60-(3H,d,J = 6.8), 2.15 - 1.05(10H,m), 1.26(3H,t,J = 7)

Preparation 47

Ethyl 4-{(5-hydroxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}butyrate

According to the same procedure as in Preparation 46, a mixture of 5,7-dihydroxyspiro[2H -1-benzopyran-2,1′-cyclohexan]-4(3H)one (prepared in Preparation 19) (0.248 g, 1.0 mmol), ethyl 4-bromobutyrate (0.215 g, 1.1 mmol), anhydrous potassium carbonate (0.207 g, 1.5 mmol), and acetonitrile (3 ml) is reacted and treated. The resulting extract is concentrated and the residue is purified by silica gel column chromatography (eluent: acetone and dichlomethane, 1:50) to obtain the title compound as an oil (0.236 g, yield 64.9%).

^{1}H-NMR ($CDCl_3$) δppm: 12.00(1H,s), 5.96(2H,s), 4.14(2H,q, J=7), 4.02(2H,t,J=6.3), 2.63(2H,s), 2.48-(2H,t,J=6.8), 2.15 - 1.20(12H,m), 1.24(3H,t,J=7).

Preparation 48

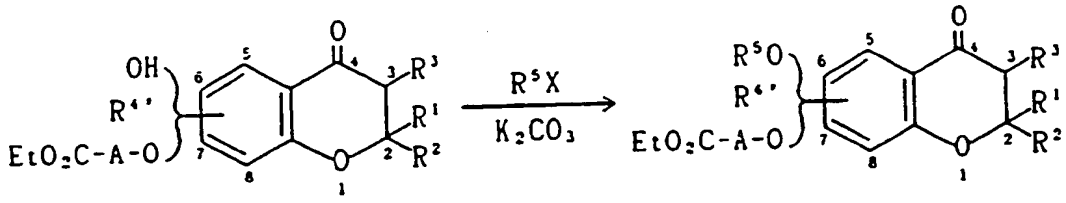
Ethyl 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclopentan]-7-yl)oxy}acetate

A mixture of ethyl 2-{(5-dihydroxy-3,4-dihydro-4-oxospiro [2H -1-benzopyran-2,1′-cyclopentan]-7-yl)-oxy}acetate (prepared in Preparation 30) (0.99 g, 3.08 mmol), methyl iodide (0.6 g, 4.26 mmol), anhydrous potassium carbonate (0.78 g, 5.65 mmol), and dry DMF (5.6 ml) is stirred at room temperature for 4 hours under nitrogen gas. DMF is removed by distillation under reduced pressure and the residue is extracted with ether. The ether layer is washed with saturated brine, dried, and concentrated. The residue is recrystallized from ether to obtain the title compound (0.89 g, yield 94.7%, m.p. = 81 - 82 °C)

Elemental analysis (for $C_{18}H_{22}O_6$)		
Calcd.:	C, 64.66;	H, 6.63
Found:	C, 64.61;	H, 6.50

^{1}H-NMR ($CDCl_3$) δppm: 6.12(1H,d,J=2), 5.95(1H,d,J=2), 4.61(2H,s), 4.28(2H,q,J=7), 3.87(3H,s), 2.72-(2H,s), 2.2 - 1.3(8H,m), 1.3(3H,t,J=7).

Preparations 49 - 62



(VI′) (VII)

In Preparations 49 to 62, corresponding compounds (VII) were prepared according to the procedure of Preparation 48 employing the starting compound (VI′) and reaction conditions given in Table 7. Purification was conducted by means of silica gel column chromatography. Physicochemical properties of each product are shown in Table 8.

Table 7

Compd. of Prep. No.	VI' material	VI' amount	Alkylating agent R^5X	potassium carbonate amount (mmol)	DMF (ml)	Reaction conditions: Temp. (°C)	Time (hr.)	Chromato Eluent	VII: R^1	R^2	R^3	$R^{4'}$	A	R^5	position of $-OR^5$	Yield (%)
48	30	2.81	MeI	4.26	5.65	5.6	25	4	----	$-(CH_2)_4-$	H	H	CH_2	Me	5	95
49	31	1.76	MeI	2.29	3.52	3.5	25	3	----	$-(CH_2)_5-$	H	H	CH_2	Me	5	88
50	31	1.49	EtI	1.79	3.0	3	25	16	----	$-(CH_2)_5-$	H	H	CH_2	Me	5	98
51	31	1.49	$PhCH_2Br$	1.80	3.0	3	25	16	ethyl acetate-dichloromethane 1:9	$-(CH_2)_5-$	H	H	CH_2	$-CH_2Ph$	5	95
52	31	1.49	i-PrI	3.0	4.5	3	25	48	ethyl acetate-dichloromethane 1:9	$-(CH_2)_5-$	H	H	CH_2	i-Pr	5	80
							60-65	8								
53[e]	31[b]	1.0	$CH_2=CHCH_2Br$	1.20	1.20	5	25	20	----	$-(CH_2)_5-$	H	H	CH_2	$CH_2CH=CH_2$	5	89
54	31	3.0	$PhCH_2O(CH_2)_2OTs$	3.45	3[c]	7	65-70	20	ethyl acetate-hexane 1:2	$-(CH_2)_5-$	H	H	CH_2	$(CH_2)_2OCH_2Ph$	5	70
55	46	0.82	MeI	1.07	1.64	3	25	23	acetone-dichloromethane 1:9 – 1:20	$-(CH_2)_5-$	H	H	$CH(CH_3)$	Me	5	85
56	47	0.65	MeI	1.3	0.85	2	25	1.5	acetone-dichloromethane 1:99-1:20	$-(CH_2)_5-$	H	H	$(CH_2)_3$	Me	5	93
57	33	1.12	MeI	1.7	1.7	3	25	4	ethyl acetate-dichloromethane 1:9	$-(CH_2)_5-$	Me	H	CH_2	Me	5	100

Table 7 (continued)

VI'							Reaction conditions			VII								
Compd of Prep. No.	material	mmol	Alkylating agent R^5X	mmol	potassium carbonate (mmol)	DMF (ml)	Temp. (°C)	Time (hr.)	Chromato Eluent	R^1	R^2	R^3	$R^{4'}$	A	R^5	position of $-OR^5$	position of -O-A-COOEt	Yield (%)
58	35	1.72	MeI	2.24	3.5	3.5	25	16	ether acetate-dichloromethane 1:9	$-(CH_2)_5-$		H	8-Me	CH_2	Me	5	7	99
59	39	2.40	MeI	3.12	4.80	4.8	25	5	--	H	H	H	H	CH_2	Me	5	7	91
60	44	3.40	MeI	5.11	6.81	7	25	17	acetonitrile-dichloromethane 1:4	Me	Me	H	H	CH_2	Me	5	7	76
61	45-3	1.25	MeI	1.88	1.88	2	25	2	ether acetate-dichloromethane 1:9	$-(CH_2)_5-$		H	H	CH_2	Me	8	7	72
62	45-2	1.25	MeI	1.88	1.88	2	25	2	---	$-(CH_2)_5-$		H	H	CH_2	Me	7	8	98

a) : Methyl ester

b) : Methyl ester

c) : NaH

Table 8

Compd. of Prep. No.	M.p. °C (recrystallized)	Molecular formula	Elemental analysis (found) C	H	^{1}H-NMR CDCℓ$_3$ δ ppm(J Hz)
48	81-82 ether	$C_{18}H_{22}O_6$	64.66 (64.61)	6.63 (6.50)	6.12(1H, d, J=2.0), 5.95(1H, d, J=2.0), 4.61(2H, s), 4.28(2H, q, J=7.0), 3.87(3H, s), 2.72(2H, s), 2.2-1.3(8H, m), 1.30(3H, t, J=7.0)
49	67-68 ether-hexane	$C_{19}H_{24}O_6$	65.50 (65.21)	6.94 (7.16)	6.12(1H, d, J=2.2), 5.98(1H, d, J=2.2), 4.61(2H, s), 4.28(2H, q, J=7.0), 3.86(3H, s), 2.61(2H, s), 2.1-1.2(13H, m)
50	thick syrup				6.10(1H, d, J=2.0), 5.58(1H, d, J=2.0), 4.60(2H, s), 4.28(2H, q, J=7.0), 4.15(2H, q, J=7.0), 2.60(2H, s), 2.0-1.1(16H, m)
51	86-87 ether-hexane	$C_{25}H_{28}O_6$	70.74 (70.67)	6.65 (6.66)	7.7 7.2(5H, m), 6.17(1H, d, J=2.0), 6.10(1H, d, J=2.0), 5.60(2H, s), 4.57(2H, s), 4.24(2H, q, J=7.0), 2.61(2H, s), 2.1-1.1(13H, m)
52	thick syrup				6.10(1H, d, J=2.0), 5.97(1H, d, J=2.0), 4.62(2H, s), 4.45(1H, m), 4.30(2H, q, J=7.0), 2.57(2H, s), 2.1-1.1(19H, m)
53	75-76 ethyl acetate-hexane	$C_{20}H_{24}O_6$	66.65 (66.44)	6.71 (6.66)	6.17-5.98(1H, m), 6.10(1H, d, J=2.4), 5.98(1H, d, J=2.4), 5.64(1H, bd, J=17.2), 5.32(1H, bd, J=10.6), 4.63(2H, s), 4.60-4.50(2H, m), 3.83(3H, s), 2.62(2H, s), 2.1-1.2(10H, m)
54	83-84 ether	$C_{27}H_{32}O_7$	69.21 (69.26)	6.88 (6.93)	7.4-7.25(5H, m), 6.13(1H, d, J=2.3), 6.01(1H, d, J=2.3), 4.72(2H, s), 4.59(2H, s), 4.27(2H, q, J=7.0), 4.16(2H, bt), 3.89(2H, bt), 2.60(2H, s), 2.0-1.3(13H, m)
55	thick syrup				6.07(1H, d, J=2.2), 5.93(1H, d, J=2.2), 4.76(1H, q, J=6.5), 4.22(2H, q, J=6.8), 3.96(3H, s), 2.60(2H, s), 1.62(3H, d, J=6.5), 2.2-1.2(13H, m)
56	thick syrup				6.03(2H, s), 4.3-3.95(4H, m), 3.86(3H, s), 2.60(2H, s), 2.50(2H, t, J=6.5), 2.3-1.1(15H, m)
57	thick syrup				6.16(1H, d, J=2.0), 6.01(1H, d, J=2.0), 4.63(2H, s), 4.30(2H, q, J=7.0), 3.87(3H, s), 2.55(1H, q, J=7.0), 2.1-1.1(16H, m)
58	100-101 ether-hexane	$C_{20}H_{26}O_6$	66.28 (66.17)	7.23 (7.08)	5.84(1H, s), 4.63(2H, s), 4.25(2H, q, J=7.0), 2.62(2H, s), 2.08(3H, s), 2.1-1.2(13H, m)

Table 6 (continued)

Compd. of Prep. No.	M.p. °C (recrystallized)	Molecular formula	Elemental analysis (found) C	Elemental analysis (found) H	^{1}H-NMR $CDCl_3$ δ ppm(J Hz)
59	97.5-98.5 benzene-hexane	$C_{14}H_{18}O_6$	59.99 (59.98)	5.75 (5.87)	6.13(1H, d, J=2.0), 5.97(1H, d, J=2.0), 4.60(2H, s), 4.42(2H, t, J=6.5), 4.26(2H, q, J=7), 3.87(3H, s), 2.70(2H, t, J=6.5), 1.30(3H, t, J=7)
60	97-98 ether	$C_{16}H_{20}O_6$	62.33 (62.22)	6.53 (6.50)	6.14(1H, d, J=2.0), 5.95(1H, d, J=2.0), 4.61(2H, s), 4.28(2H, q, J=7.0), 3.88(3H, s), 2.64(2H, s), 1.40(6H, s), 1.30(3H, t, J=7.0)
61	100-101 ether				7.55(1H, d, J=9.0), 6.45(1H, d, J=9.0), 4.76(2H, s), 3.95(3H, s), 3.80(3H, s), 2.67(2H, s), 2.15-1.2(10H, m)
62	46-47 ether-hexane				7.60(1H, d, J=9.0), 6.57(1H, d, J=9.0), 4.68(2H, s), 3.91(3H, s), 3.82(3H, s), 2.67(2H, s), 2.1-1.2(10H, m)

Preparation 63

Ethyl 4-{(5-(2-hydroxy)ethyl-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}acetate

A solution of ethyl 4-{(5-(2-benzyloxy)ethyl-3,4-dihydro-4-oxospiro-[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}acetate(prepared in Preparation 54) (0.347 g, 0.74 mmol) in a mixture of ethyl acetate and ethanol (1:3) (7 ml) is hydrogenated over 10% Palladium on activated carbon at room temperature until theoretical amount of hydrogen is consumed. The catalyst is removed by filtration and the filtrate is concentrated. The residue is placed on a silica gel column and eluted with a mixture of ethyl acetate and dichloromethane (1:9) to yield the title compound as a crude crystalline solid (0.235 g, 84%). Recrystallization from diethyl ether gives a product having a melting point of 104 - 105 °C.

Elemental analysis (for $C_{20}H_{26}O_7$)		
Calcd.:	C, 63.48;	H, 6.92
Found:	C, 63.37;	H, 6.95

^{1}H-NMR ($CDCl_3$) δppm: 6.14(1H,d,J = 2.3), 6.05(1H,d,J = 2.3), 4.62(2H,s), 4.29(2H,q,J = 7), 4.2-3.8(4H,m), 2.63(2H,s), 2.1 - 1.2(10H,m), 1.30(3H,t,J = 7).

Preparation 64

Ethyl 2-{(6-chloro-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}acetate

Ethyl 2-{(3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}acetate (prepared in Preparation 28) (0.72 g, 2.26 mmol) is dissolved in dry dichloromethane (7.2 ml). To the solution is added dropwise 1 M sulfuryl chloride solution in dichloromethane (2.3 ml, 2.3 mmol) at -40 °C with stirring. After 2 hours stirring at -40 to -10 °C, the solvent is removed by distillation. The residue is dissolved in dichloromethane, and the solution is washed with water, dried, and concentrated. The residue is applied to a Lober column and eluted with a mixture of ethyl acetate and hexane (1:2). The resulting crude product is recrystallized from a mixture of diethyl ether and hexane to yield the title compound (0.6 g, yield 75%, m.p. = 116 - 117 °C).

Elemental analysis (for $C_{18}H_{21}ClO_5$)			
Calcd.:	C, 61.28;	H, 6.00;	Cl, 10.05
Found:	C, 61.30;	H, 6.13;	Cl, 10.13

^{1}H-NMR ($CDCl_3$) δppm: 7.86(1H,s), 6.36(1H,s), 4.72(2H,s), 4.27(2H,q,J = 7), 2.63(2H,s), 2.1 - 1.1(13H,m).

Preparation 65

Ethyl 2-{(6,8-dichloro-5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)-oxy}acetate (65-1), Ethyl 2-{(6-chloro-5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan-7-yl)oxy}acetate (65-2), and Ethyl 2-{(8-chloro-5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}acetate (65-3)

Ethyl 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1'-cyclohexan]-7-yl)oxy}acetate (prepared in Preparation 49) (0.64 g, 1.83 mmol) is dissolved in dry dichloromethane (11 ml). To the solution is added dropwise 1 M sulfuryl chloride solution in dichloromethane (2.0 ml) at -30 to -25 °C with stirring. After 15 minutes stirring at the same temperature, the solvent is removed by distillation. The residue is applied to a Lober column and eluted with a mixture of ethyl acetate and dichloromethane (1:9). From the earlier fractions, the compound (65-1) (50 mg, yield 6.5%) is obtained. Recrystallization from hexane gives a compound having a melting point of 87 - 88 °C. From the succeeding fractions, the compound (65-2) (0.233 g, yield 33.1%) is obtained. Recrystallization from a mixture of diethyl ether and hexane gives a compound having a melting point of 104 - 105 °C. From the last fraction, the compound (65-3) (0.394 g, yield 56%) is obtained.
Recrystallization from a mixture of benzene and hexane gives the compound having a melting point of 129 - 130 °C.

Compound (65-1)

Elemental analysis (for $C_{19}H_{22}Cl_2O_6$)			
Calcd.:	C, 54.69;	H, 5.31;	Cl, 16.99
Found:	C, 54.77;	H, 5.42;	Cl, 17.10

^{1}H-NMR ($CDCl_3$) δppm: 4.70(2H,s), 4.30(2H,q,J = 7), 3.88(3H,s), 2.69(2H,s), 2.2 - 1.25(13H,m).

Compound (65-2)

Elemental analysis (for $C_{19}H_{23}ClO_6$)			
Calcd.:	C, 59.61;	H, 6.05;	Cl, 9.26
Found:	C, 59.63;	H, 5.93;	Cl, 9.19

^{1}H-NMR ($CDCl_3$) δppm: 6.20(1H,s), 4.72(2H,s), 4.28(2H,q,J = 7), 3.88(3H,s), 2.62(2H,s), 2.1 - 1.2(13H,m).

Compound (65-3)

Elemental analysis (for $C_{19}H_{23}ClO_6$)			
Calcd.:	C, 59.61;	H, 6.05;	Cl, 9.26
Found:	C, 59.59;	H, 6.02;	Cl, 9.05

^{1}H-NMR ($CDCl_3$) δppm: 6.02(1H,s), 4.76(2H,s), 4.27(2H,q,J = 7), 3.85(3H,s), 2.62(2H,s), 2.2 - 1.2(13H,m).

Preparation 66

Ethyl 2-{(8-chloro-5-hydroxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1'-cyclohexan-7-yl)oxy}acetate

Ethyl 2-{(8-chloro-5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1'-cyclohexan]-7-yl)-oxy}acetate (65-3, prepared in Preparation 65) (0.575 g, 1.50 mmol) is dissolved in dry dichloromethane (3 ml). To the solution is added dropwise a 2 M boron trichloride solution in dichloromethane (1.5 ml, 3.0 mmol) at -75 to -70 °C. After stirring at -70 to -50 °C for 1.5 hours, ice-cold water is added thereto and the

mixture is extracted with dichloromethane. The organic layer is separated, washed with aqueous sodium bicarbonate, dried, and concentrated. The residue is applied to a silica gel column and eluted with a mixture of acetonitrile and dichloromethane (1:9) to yield the title compound as a crystalline solid (0.428 g, yield 77.4%). Recrystallization from diethyl ether gives a product having a melting point of 110 - 111 °C.

Elemental analysis (for $C_{18}H_{20}ClO_6$)			
Calcd.:	C, 58.62;	H, 5.74;	Cl, 9.61
Found:	C, 58.60;	H, 5.69;	Cl, 9.73

^{1}H-NMR ($CDCl_3$) δppm: 10.95(1H,s), 5.94(1H,s), 4.71(2H,s), 4.28(2H,q,J=7), 2.69(2H,s), 2.2 - 1.2-(13H,m).

Preparation 67

Ethyl 2-{(6-chloro-5-hydroxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan-7-yl)oxy}acetate

According to the procedure of Preparation 66 employing ethyl 2{(6-chloro-5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy} acetate (65-2, prepared in Preparation 65) (0.65 g, 1.7 mmol) and 2 M boron trichloride solution in dichloromethane (1.7 ml, 3.4 mmol), the title compound is prepared as a crystalline solid (0.62 g, yield 94%). Recrystallization from cyclohexane gives a product having a melting point of 103 - 104 °C.

Elementary analysis (for $C_{18}H_{20}ClO_6$)			
Calcd.:	C, 58.62;	H, 5.74;	Cl, 9.61
Found:	C, 58.53;	H, 5.67;	Cl, 9.78

^{1}H-NMR ($CDCl_3$) δppm: 12.4(1H,s), 5.94(1H,s), 4.72(2H,s), 4.28(2H,q,J=7), 2.69(2H,s), 2.2 - 1.2(13H,m).

Preparation 68

Ethyl 2-{(6,8-dichloro-5-hydroxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan-7-yl)oxy}acetate

According to the procedure of Preparation 66 employing ethyl 2-{(6,8-dichloro-5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan-7-yl)oxy}acetate (65-1, prepared in Preparation 65) (0.635 g, 1.52 mmol) and 2 M boron trichloride solution in dichloromethane (1.7 ml, 3.4 mmol), the title compound is prepared as a crystalline solid (0.60 g, yield 98%). Recrystallizaton from a mixture of diethyl ether and hexane gives a product having a melting point of 134 - 135 °C.

Elemental analysis (for $C_{18}H_{20}Cl_2O_6$)			
Calcd.:	C, 53.61;	H, 5.00;	Cl, 17.59
Found:	C, 53.34;	H, 4.98;	Cl, 17.42

^{1}H-NMR ($CDCl_3$) δppm: 12.35(1H,s), 4.70(2H,s), 4.29(2H,q,J=7), 2.74(2H,s), 2.2 - 1.2(13H,m).

Preparation 69

Ethyl 2-{(5-methoxy-8-nitro-3,4-dihydro-4oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}acetate

Ethyl 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}acetate (prepared in Preparation 49) (1.3 g, 3.92 mmol) is added by portions to fuming nitric acid (d= 1.50, 10 ml) at -60 °C with stirring. After one hour stirring at -60 to -40 °C, the reaction mixture is poured into ice-cold water. The mixture is extracted with diethyl ether. The ether layer is separated, washed with water and then aqueous sodium bicarbonate, dried, and concentrated. The residue is washed with diethyl ether. Recrystallization from a mixture of ethyl acetate and hexane gives the title compounds as a crystalline solid (1.05 g, yield 74.2%, m.p.= 142 - 143 °C).

Elemental analysis (for $C_{19}H_{23}NO_8$)			
Calcd.:	C, 58.00;	H, 5.89;	N, 3.56
Found:	C, 57.93;	H, 5.89;	N, 3.60

^{1}H-NMR ($CDCl_3$) δppm: 5.99(1H,s), 4.74(2H,s), 4.26(2H,q,J=7), 3.89(3H,s), 2.65(2H,s), 2.1 - 1.2(13H,m).

Preparation 70

Ethyl 2-{(5-methoxy-8-chlorosulfonyl-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy} acetate

To a solution of ethyl 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)-oxy} acetate (prepared in Preparation 49) (0.80 g, 2.29 mmol) in dry dichloromethane (6 ml) is added chlorosulfonic acid (1.6 g, 13.7 mmol) with stirring while cooling on ice. After 1.5 hours reaction at room temperature, chlorosulfonic acid (0.54 g, 4.64 mmol) is added thereto and the reaction is continued at room temperature for additional 0.5 hours. To the mixture is added thionyl chloride (1.09 g, 9.16 mmol) and the mixture is heated to reflux for 1.5 hours. The reaction mixture is poured into ice-cold water, and the solution is stirred for 10 minutes, and extracted with ethyl acetate. The ethyl acetate layer is separated and washed with saturated brine, dried, and concentrated to yield the title compound as a crystalline solid (0.99 g, yield 96%, m.p.= 74 - 78 °C). The product is employed in the next step without purification.

Preparation 71

Ethyl 2-{(5-methoxy-8-sulfamoyl-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)-oxy}acetate

A solution of ethyl 2{(5-methoxy-8-chlorosulfonyl-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}acetate (prepared in Preparation 70) (0.32 g, 0.74 mmol) in dichloromethane (4 ml) is added dropwise to a solution of liquid ammonia (2 ml, 80 mmol) and triethylamine (0.1 ml, 0.7 mmol) in dichloromethane (4 ml) at -25 to -20 °C. After stirring at the same temperature for 30 minutes, the solvent is removed by distillation. The residue is placed on a silica gel column and eluted with a mixture of acetone and dichloromethane (1:1) to yield the title compound as a crystalline solid (0.173 g, yield 56.5%). Recrystallization from a mixture of ethyl acetate and ether gives a product having a melting point of 188 - 190 °C.

Elemental analysis (for $C_{19}H_{25}NO_8S$)				
Calcd.:	C, 53.39;	H, 5.89;	N, 3.28;	S, 7.50
Found:	C, 53.19;	H, 5.90;	N, 3.20;	S, 7.56

^{1}H-NMR ($CDCl_3$) δppm: 5.96(1H, S), 5.88(2H,s), 4.78(2H,s), 4.34(2H,q,J = 7), 3.94(3H,s), 2.66(2H,s), 2.15 - 1.2(10H,m), 1.34(3H,t,J = 7).

Preparation 72

Ethyl 2-{(5-methoxy-8-N -methylsulfamoyl-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)-oxy}acetate

To a solution of ethyl 2-{(5-methoxy-8-chlorosulfonyl-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}acetate (prepared in Preparation 70) (0.30 g, 0.70 mmol), triethylamine (0.87 ml, 6.2 mmol) in acetone (6.7 ml) is added dropwise a 30% methylamine solution in ethanol (0.181 g, 1.5 mmol) at -30 to -20 °C over 10 minutes. After 30 minutes stirring at the same temperature, the solvent is removed by distillation. The residue is dissolved in ethyl acetate. The solution is washed with dilute hydrochloric acid and then saturated brine, dried, and concentrated. The residue is placed on silica gel column and eluted with a mixture of ethyl acetate and dichloromethane (1:1) to yield the title compound as crystalline solid (0.244 g, yield 82.4%). Recrystallization from ethyl acetate gives a product having a melting point 177 - 178 °C.

Elemental analysis (for $C_{20}H_{27}NO_8S$)				
Calcd.:	C, 54.41;	H, 6.16;	N, 3.17;	S, 7.26
Found:	C, 54.17;	H, 6.06;	N, 3.19;	S, 7.12

^{1}H-NMR($CDCl_3$) δppm: 6.17(1H,q,J = 5.2), 5.95(1H,s), 4.76(2H,s), 4.34(2H,q,J = 7.2), 3.94(3H,s), 2.70-(3H,d,J = 5.2), 2.66(2H,s)', 2.15 - 1.2(10H,m), 1.35(3H,t,J = 7.2).

Preparation 73

Ethyl 2-{(5-methoxy-8-N , N -dimethylsulfamoyl-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan-7-yl)oxy}acetate

A solution of ethyl 2-{(5-methoxy-8-chlorosulfonyl-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}acetate (prepared in Preparation 70) (0.35 g, 0.81 mmol) in acetone (7 ml) is added dropwise to a mixture of 50% aqueous dimethylamine (0.085 g, 0.94 mmol), acetone (2 ml), and triethylamine (0.096 g, 0.95 mmol) at -30 °C. The mixture is stirred at -30 to -20 °C for 20 minutes. The reaction mixture is treated in the same maneer as in Preparation 72. The resulting residue is chromatographed (eluent: acetone and dichloromethane, 1:1) to yield the title compound as a crystalline solid (0.30 g, yield 84.1%). Recrystallization from diethyl ether gives a product having a melting point of 237 - 238 °C.

Elemental analysis (for $C_{21}H_{29}NO_8S$)				
Calcd.:	C, 55.37;	H, 6.42;	N, 3.07;	S, 7.04
Found:	C, 55.20;	H, 6.30;	N, 3.06;	S, 6.74

^{1}H-NMR ($CDCl_3$) δppm: 5.93(1H, s), 4.78(2H, s), 4.28(2H,q,J = 7.2), 3.90(3H, s), 2.92(6H, s), 2.66(2H, s), 2.1 - 1.2 (10H,m), 1.3(2H,t,J = 7.2).

Preparation 74

Ethyl 2-{(7-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-5-yl)oxy}acetate

To a solution of 5,7-dimethoxy-spiro[[2H -1-benzopyran-2,1′-cyclohexan]-4(3H)-one (prepared in Preparation 8) (0.70 g, 2.54 mmol) in dry dichloromethane (5 ml) is added dropwise 2 M boron trichloride solution in dichloromethane (3 ml, 6 mmol) at -35 °C. After one hour stirring at -30 to 0 °C, ice-cold water is added to the mixture and the mixture is extracted with dichloromethane. The dichloromethane layer is washed with water, dried, and concentrated to yield 5-hydroxy-7-methoxyspiro[2H -1-benzopyran-2,1′-cyclohexan]-4-(3H)-one as a crude crystalline solid (0.66 g, 99.5%). Recrystallization from hexane gives a product having a melting point of 69 - 70 °C.

A mixture of the above compound (0.71 g, 2.71 mmol), ethyl bromoacetate (0.542 g, 3.69 mmol), sodium iodide (0.02 g, 0.13 mmol), anhydrous potassium carbonate (0.56 g, 4.06 mmol) and DMF (9 ml) is stirred three overnights at room temperature. The mixture is treated in the same manner as in Preparation 27 to yield the title compound as a thick syrup (0.80 g, yield 85%).

^{1}H-NMR ($CDCl_3$) δppm: 6.10(1H,d,J = 2), 5.89(1H,d,J = 2), 4.64(2H,s), 4.25(2H,q,J = 7), 3.78(3H,s), 2.61-(2H,s), 2.1 - 1.2(13H,m).

Preparation 75

(4′-Acetylamino-2′,6′-dimethoxyphenyl)ethanone (75-1), (4′-acetylamino-2′-hydroxy-6′-methoxyphenyl)-ethanone (75-2), and (2′-acetylamino-4′,6′-dimethoxyphenyl)ethanone (75-3)

To a solution of acetyl chloride (9.42 g, 0.12 mol) in dry dichloromethane (200 ml) is added anhydrous aluminium chloride (26.68 g, 0.2 mol) at room temperature with stirring and reacted for 0.5 hours, which is followed by the addition of N -3′,5′ dimethoxyphenylacetamide (18.2 g, 0.093 mol) keeping the temperature below 10 °C. After 1.5 hours reaction at room temperature, the mixture is diluted with dichloromethane, poured into 10% ice-cooled hydrochloric acid, and extracted with dichloromethane. The dichloromethane layer is washed with water, dried, and the solvent is removed by distillation. The residue is placed on a silica gel column and eluted with a mixture of ethylacetate and dichloromethane (1:1). From the earlier fraction, the title compound (75-3) (4.2 g, 19%) is obtained. From the succeeding fractions, the title compound (75-2) (2.23 g, 11%) and (75-1) (12.3 g, 50%) are obtained, successively. Each compound is employed to the next step without purification.

Compound (75-1) ; m.p. = 194 - 195 °C

Elemental analysis (for $C_{12}H_{15}NO_4$)			
Calcd.:	C, 60.76;	H, 6.37;	N, 5.90
Found:	C, 60.41;	H, 6.24;	N, 5.88

^{1}H-NMR ($CDCl_3$) δppm: 8.15(1H,b), 6.80(2H,s), 3.70(6H,s), 2.45(3H,s), 2.12(3H,s).

Compound (75-2) ; m.p. = 196 - 197 °C

Elemental analysis (for $C_{11}H_{13}NO_4$)			
Calcd.:	C, 59.19;	H, 5.87;	N, 6.28
Found:	C, 59.00;	H, 5.78;	N, 6.13

^{1}H-NMR ($CDCl_3$) δppm: 13.57(1H,s), 7.50(1H,b), 7.10(1H,d,J = 1.5), 6.31(1H,d,J = 1.5), 3.85(3H,s), 2.60(3H,s), 2.17(3H,s).

Compound (75-3) ; m.p. = 105 - 106 °C

Elemental analysis (for $C_{12}H_{15}NO_4$)			
Calcd.:	C, 60.76;	H, 6.37;	N, 5.90
Found:	C, 60.74;	H, 6.30;	N, 5.76

^{1}H-NMR ($CDCl_3$) δppm: 11.70(1H,b), 8.00(1H,d,J = 3), 6.18(1H,d,J = 3), 3.81(6H,s), 2.56(3H,s), 2.18(3H,s).

Preparation 76

(4′-Amino-2′,6′-dimethoxyphenyl)ethanone

A mixture of (4′-acetylamino-2′,6′-dimethoxyphenyl)ethanone (compound 75-1) (7.11 g, 0.03 mol) and 10% potassium hydroxide solution in ethanol is heated to reflux for 3 hours. The solvent is distilled from the reaction mixture under reduced pressure. The residue is dissolved in dichloromethane, and the solution is washed with water, dried, and concentrated. The residue is placed on a silica gel column and eluted with a mixture of ethylacetate and dichloromethane (1:1) to yield the title compound as a crystalline solid (5.54 g, 95%, m.p. = 154 -155 °C).

Elemental analysis (for $C_{10}H_{13}NO_3$)			
Calcd.:	C, 61.53;	H, 6.71;	N, 7.18
Found:	C, 61.50;	H, 6.69;	N, 7.20

^{1}H-NMR ($CDCl_3$) δppm: 5.86(2H,s), 3.76(2H,b), 3.76(6H,s), 2.43(3H,s).

Preparation 77

(4′,6′-Dimethoxy-2′-mercaptophenyl)ethanone

A solution of (2′-hydroxy-4′,6′-dimethoxyphenyl) ethanone (Table 1, literature No. d) (8 g, 40.8 mmol) in dry DMF (31 ml) is added dropwise to a suspension of 60% sodium hydride (1.71 g, 42.8 mmol) in DMF (10 ml) under ice-cooling under nitrogen atmosphere. After 5 minutes stirring at room temperature, N,N-dimethylthiocarbamoyl chloride (6.55 g, 53 mmol) is added to the mixture. The mixture is heated at 55 to 60 °C for one hour with stirring. To the reaction mixture is added ice-cooled saturated aqueous ammonium chloride solution. The mixture is extracted with a mixture of ethyl acetate and dichloromethane (2:1). The extract is washed with saturated brine, dried, and the solvent is removed by distillation. The residue is treated with diethyl ether, and the mixture is filtered to obtain a crystalline solid (4.84 g). The mother liquror is applied to a silica gel column. The column is developed with a mixture of ethyl acetate and dichloromethane (1:9) to obtain an additional crystalline solid (1.43 g). The overall yield of O-(2-acetyl-3,5-dimethoxyphenyl)-N , N -dimethylthiocarbamate is 6.25 g (54%).

This crystal (3.0 g, 11.2 mmol) is dissolved in diphenyl ether (30 ml) and the solution is heated at 220 to 230 °C for one hour with stirring under nitrogen gas. Diphenyl ether is removed under reduced pressure. The residue is placed on a silica gel column and eluted with a mixture of ethyl acetate and dichloromethane (1:9) to obtain S-(2-acetyl-3,5-dimethoxyphenyl)-N , N -dimethylthiocarbamate as a thick syrup (1.0 g, yield 33%).

A solution of the thick syrup (1.0 g, 3.75 mmol) and 2 N sodium hydroxide (2.3 ml) in methanol (10 ml) is heated to ref lux for one hour under nitrogen gas. After the mixture is made acidic with dilute hydrochloric acid, methanol is removed under reduced pressure and the residue is extracted with diethyl ether. The

extract is washed with saturated brine, dried, and the solvent is removed by distillation. The residue is placed on a silica gel column and eluted with a mixture of ethyl acetate and dichloromethane (1:9). The eluate is again applied to a silica gel column and eluted with a mixture of ethyl acetate and benzene (1:9) to obtain the title compound as a crystalline solid (0.56 g, yield 76%, m.p. = 57 - 59 °C).

^{1}H-NMR($CDCl_3$) δppm: 6.42(1H,d,J = 2.2), 6.26(1H,d,J = 2.2), 4.12(1H,s), 3.85(3H,s), 3.82(3H,s), 2.54-(3H,s).

Preparation 78

5,7-Dimethoxyspiro[2H -1-benzothiin-2,1′-cyclohexan]-4(3H)-one

A solution of (4′,6′-dimethoxy-2′-mercaptophenyl) ethanone (prepared in Preparation 77) (0.53 g, 2.5 mmol) and cyclohexanonepyrrolidine enamine (0.57 g, 3.73 mmol) in dry methanol (8 ml) is heated to reflux for 3 hours under nitrogen gas. The solvent is removed by distillation and the residue is dissolved in diethyl ether. The solution is washed with dilute hydrochloric acid and then with saturated brine, dried, and the solvent is removed. The residue is placed on a silica gel column and eluted with a mixture of ethyl acetate and dichloromethane (1:9). The starting material (0.142 g, 26%) and the title compound (crystalline solid, 0.526 g, 71.9%) are obtained, successively. Recrystallization from diethyl ether gives the title compound having a melting point of 104 - 105 °C.

Elemental analysis (for $C_{16}H_{20}O_3S$)			
Calcd.:	C, 65.72;	H, 6.89;	S, 10.96
Found:	C, 65.73;	H, 6.90;	S, 10.67

^{1}H-NMR ($CDCl_3$) δppm: 6.35(1H,d,J = 2.2), 6.20(1H,d,J = 2.2), 3.86(3H,s), 3.82(3H,s), 2.88(2H,s), 1.95- 1.20-(10H,m).

Preparation 79

5,7-Dihydroxyspiro[2H -1-benzothiin-2,1′-cyclohexan]-4(3H)-one

A mixture of 5,7-Dimethoxyspiro[2H -1-benzothiin -2,1′-cyclohexan]-4-(3H)-one (prepared in Preparation 78) (0.526 g, 1.80 mmol) and pyridine hydrochloride (4 g, 34.6 mmol) is heated at 205 - 210 °C for 50 minutes with stirring under nitrogen gas. After cooling, dilute HCl is added to the mixture. The mixture is extracted with diethyl ether. The extract is washed with saturated brine, dried, and the solvent is removed. The residue is placed on a silica gel column and eluted with a mixture of ethyl acetate and dichloromethane (1:9) to obtain the title compound as a crystalline solid (0.459 g, 96%). Recrystallization from diethyl ether gives a product having a melting point of 160 - 162 °C. ^{1}H-NMR ($CDCl_3$) δppm: 13.04(1H,s), 7.5(1H,b), 6.27(1H,d,J = 2.2), 6.08(1H,d,J = 2.2), 2.87(2H,s), 2.0 - 1.1(10H,m).

Preparation 80

5,7-Dimethoxyspiro[1,2,3,4-tetrahydroquinoline-2,1′-cyclohexan]-4-one

A mixture of (2′-acetylamino-4′,6′-dimethoxyphenyl)ethanone (compound 75-3, prepared in Preparation 75) (0.237 g, 1.0 mmol), potassium hydroxide (0.2 g, 3.57 mmol), water (0.2 ml), and ethanol (2 ml) is heated to reflux for one hour. The solvent is distilled under reduced pressure, and the residue is extracted with dichloromethane. The extract is washed with water, dried, and the solvent is removed to yield a crystalline residue. Recrystallization from ethyl acetate gives (2′-amino-4′,6′-dimethoxyphenyl)ethanone as a crystalline solid (0.114 g, 58%, m.p. = 104 - 105 °C).

To a solution of (2′-amino-4′,6′-dimethoxyphenyl) ethanone (3.25 g, 16.7 mmol) in absolute methanol (300 ml) is added cyclohexanonepyrrolidine enamine (5.54 g, 36.2 mmol) and pyrrolidine (2.37 g, 33.4 mmol). The mixture is heated to reflux for 65 hours under argon gas, then the solvent is removed under reduced pressure. Ethyl acetate and diethyl ether are added to the residue and the mixture is filtered to remove insoluble matter including starting materials (0.87 g). The ethyl acetate layer is separated, washed, dried and the solvent is removed by distillation. The residue is placed on a silica gel column and eluted with a mixture of acetone and dichloromethane (1:5) to obtain the title compound as a crystalline solid (0.88 g, 20%). Recrystallization from a mixture of dichloromethane and diethyl ether gives a product having a melting point of 168 - 169 °C.

Elemental analysis (for $C_{16}H_{21}NO_3$)			
Calcd.:	C, 69.80;	H, 7.69;	N, 5.09
Found:	C, 69.65;	H, 7,57;	N, 4.98

^{1}H-NMR ($CDCl_3$) δppm: 5.77(1H,d,J = 2.2), 5.70(1H,d,J = 2.2), 4.49(1H,b), 3.84(3H,s), 3.79(3H,s), 2.57(2H,s), 2.2 - 1.2(10H,m).

Preparation 81

5,7-Dihydroxyspiro[1,2,3,4-tetrahydroquinoline-2,1′-cyclohexan]-4-one

A mixture of 5,7-dimethoxyspiro[1,2,3,4-tetrahydroquinoline-2,1′-cyclohexan]-4-one (prepared in Preparation 80) (0.422 g, 1.53 mmol) and pyridine hydrochloride (1.2 g, 10.4 mmol) is heated at 190 °C for one hour with stirring under nitrogen gas. After cooling, dilute hydrochloric acid is added to the mixture and the mixture is extracted with ethyl acetate. The extract is washed with saturated brine, dried, and the solvent is removed by distillation. The residue is placed on a silica gel column and eluted with a mixture of ethyl acetate and dichloromethane (1:3). From the earlier fractions, 5-hydroxy-7-methoxyspiro[1,2,3,4-tetrahydroquinoline-2,1′-cyclohexan]-4-one is obtained as a crystalline solid (0.098 g, 25%). From the succeeding fractions, the title compound is obtained as a crystalline solid (0.26 g, 68%). Recrystallization from diethyl ether gives a product having a melting point of 132 - 133 °C.

Elemental analysis (for $C_{14}H_{17}NO_3 \cdot 1/2H_2O$)			
Calcd.:	C, 66.65;	H, 7.46;	N, 5.18
Found:	C, 66.47;	H, 7,13;	N, 5.25

^{1}H-NMR ($CDCl_3$) δppm: 12.5(1H,s), 5.67(1H,d,J = 2.2), 5.60(1H,b), 5.56(1H,d,J = 2.2), 4.45(1H,b), 2.60-(2H,s), 1.8 - 1.2(10H,m).

Example 1

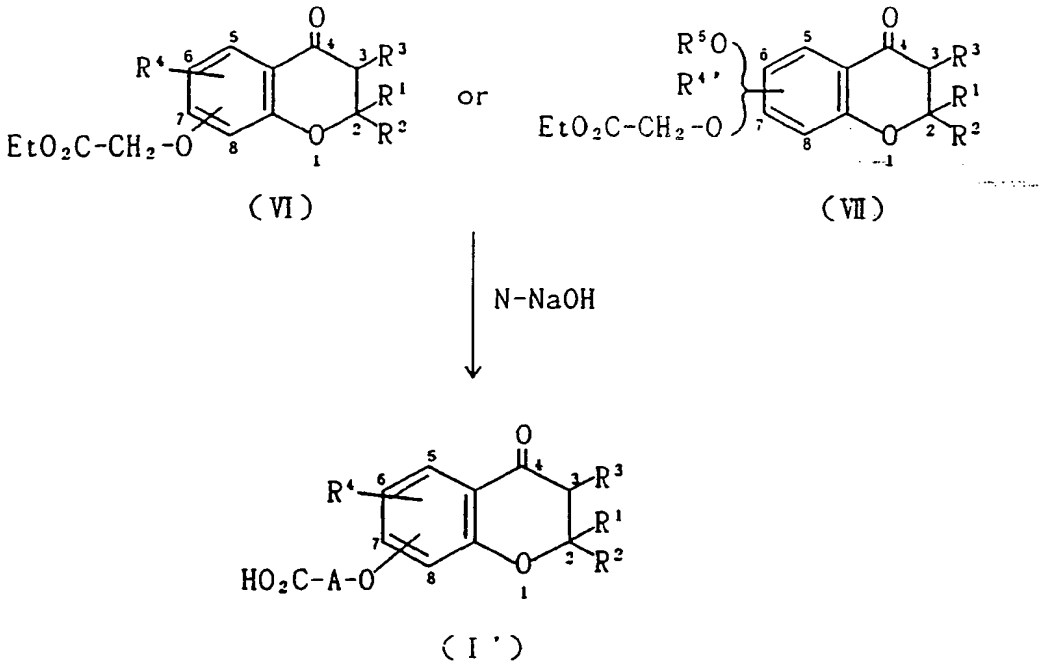
{(3,4-Dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-6yl)oxy}acetic acid

A mixture of ethyl (2-{(3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-6-yl)oxy}acetate (prepared in Preparation 27) (0.5 g, 1.57 mmol) and 1 N sodium hydroxide (1.9 ml, 1.9 mmol), and ethanol (5 ml) is stirred at room temperature for one hour. The mixture is made acidic with 1N HCl, filtered, and washed with a small amount of water to separate crystalline precipitates.
Recrystallization from a mixture of diethyl ether and hexane gives the title compound as a crystalline solid (0.39 g, 85.6%, m.p. = 148 - 149 °C.).

Elemental analysis (for $C_{16}H_{18}O_5$)		
Calcd.:	C, 66.19;	H, 6.25
Found:	C, 66.03;	H, 6.35

^{1}H-NMR (d_6-DMSO) δppm: 7.23(1H,dd,J=9,2), 7.16(1H,d,J=2), 6.99(1H,d,J=9), 4.67(2H,s), 2.74(2H,s), 2.1-1.1(10H,m).

Example 2 - 47



(VI) (VII) (I')

In Examples 2 to 47, corresponding compounds (I') were prepared according to the procedure of Example 1 employing the starting materials (VI or VII) and reaction conditions given in Table 9. Physicochemical properties of each product are shown in Table 10.

Table 9

Compound of Example No.	VI, VII		N-NaOH (mℓ)	EtOH (mℓ)	Reaction condition		I'						
	Prep. No.	mmol			Temp. (℃)	Time (hr.)	R^1 R^2	R^3	R^4	A	position of HO_2C-A-(	Yield (%)
1	27	1.57	1.9	5	25	1	-$(CH_2)_5$-	H	H	CH_2	6	86
2	28	1.87	4.5	4.5	25	1	-$(CH_2)_5$-	H	H	CH_2	7	98
3	29	1.3	2.9	4	25	0.5	Me Ph	H	5-OH	CH_2	7	82
4	30	1.87	4.5	4.5	25	1	-$(CH_2)_4$-	H	5-OH	CH_2	7	93
5	31	1.6	3.6	5	25	0.5	-$(CH_2)_5$-	H	5-OH	CH_2	7	95
6	32	3.67	8.8	16	25	0.7	-$(CH_2)_5$-	H	5-OCH_2COOH	CH_2	7	87
7	34	1.87	4.5	4.5	25	1	-$(CH_2)_5$-	H	5-Me	CH_2	7	96
8	35	1.87	4.5	4.5	25	1	-$(CH_2)_6$-	H	5-OH 8-Me	CH_2	7	91
9	36	2.86	3.4	10	25	1	-$(CH_2)_5$-	H	5-Cℓ	CH_2	7	88
10	37	1.11	1.3	8	25	1	-$(CH_2)_5$-	H	5-Cℓ 6-Cℓ	CH_2	7	90
11	38	0.77	1.0	3	25	1	-$(CH_2)_5$-	H	5-Cℓ 8-Cℓ	CH_2	7	93
12	39	1.13	2.5	10	25	1	H H	H	5-OH	CH_2	7	86
13	40	5.68	6.8	-	25	1	H H	H	H	CH_2	7	95
14	41	6.0	7.2	-	25	1	Me Me	H	H	CH_2	7	94
15	42	6.0	7.2	-	25	1	H Me	H	H	CH_2	7	90
16	43	2.15	7.6 (trifluoro acetic acid)	-	25	1	H Ph	H	H	CH_2	7	81
17	44	6.0	13.2	-	25	1	Me Me	H	5-OH	CH_2	7	92
18	45-1	4.5	9.9	19	25	1	-$(CH_2)_5$-	H	8-OCH_2COOH	CH_2	7	88
19	45-2	0.30	0.4	2	25	1	-$(CH_2)_5$-	H	7-OH	CH_2	7	100

Table 9 (continued)

Compound of Example No.	VI, VII		N−NaOH (ml)	EtOH (ml)	Reaction condition		I						
	Prep. No.	mmol			Temp. (°C)	Time (hr.)	R¹	R²	R³	R⁴	A	position of HO_2C-A-O	Yield (%)
20	48	2.66	3.2	9	25	1	-$(CH_2)_4$-		H	5-OMe	CH_2	7	95
21	49	1.40	3.0	4	25	20	-$(CH_2)_5$-		H	5-OMe	CH_2	7	92
22	50	2.66	3.2	9	25	1	-$(CH_2)_5$-		H	5-OEt	CH_2	7	90
23	51	2.66	3.2	9	25	1	-$(CH_2)_5$-		H	5-OCH_2Ph	CH_2	7	83
24	52	2.66	3.2	9	25	1	-$(CH_2)_5$-		H	5-OPr-i	CH_2	7	89
25	53	0.64	0.77	3	25	1	-$(CH_2)_5$-		H	5-$OCH_2CH=CH_2$	CH_2	7	93
26	54	0.49	0.6	2	25	1	-$(CH_2)_5$-		H	5-$O(CH_2)_2OCH_2Ph$	CH_2	7	93
27	63	0.75	0.9	5	25	1	-$(CH_2)_5$-		H	5-$O(CH_2)_2OH$	CH_2	7	90
28	55	0.85	1.0	1	25	2	-$(CH_2)_5$-		H	5-OMe	$CH(CH_3)$	7	80
29	56	0.56	1.0	1	25	17	-$(CH_2)_5$-		H	5-OMe	$(CH_2)_3$	7	45
30	57	2.66	3.2	9	25	1	-$(CH_2)_5$-		Me	5-OMe	CH_2	7	79
31	58	2.66	3.2	9	25	1	-$(CH_2)_5$-		H	5-OMe 8-Me	CH_2	7	96
32	59	1.75	2.1	5	25	1	H	H	H	5-OMe	CH_2	7	95
33	60	1.62	2.0	2	25	1	Me	Me	H	5-OMe	CH_2	7	97
34	61	1.29	1.55	5	25	2	-$(CH_2)_5$-		H	8-OMe	CH_2	7	90
35[a)]	62	0.93	1.26	3	25	2	-$(CH_2)_5$-		H	7-OMe	CH_2	8	87
36	64	1.58	1.9	6	25	0.5	-$(CH_2)_5$-		H	6-Cl	CH_2	7	99
37	65-1	1.5	3.3	4 (+dichloromethane 4)	25	1	-$(CH_2)_5$-		H	5-OMe 6-Cl, 8-Cl	CH_2	7	88
38	65-2	1.5	3.3	4	25	0.5	-$(CH_2)_5$-		H	5-OMe 6-Cl	CH_2	7	97
39	65-3	1.5	3.3	4	25	0.5	-$(CH_2)_5$-		H	5-OMe 8-Cl	CH_2	7	95
40	68	1.5	3.3	4 (+dichloromethane 4)	25	1	-$(CH_2)_5$-		H	5-OH 6-Cl, 8-Cl	CH_2	7	95
41	67	1.5	3.3	4	25	0.5	-$(CH_2)_5$-		H	5-OH 6-Cl	CH_2	7	96

Table 9 (continued)

Compound of Example No.	VI, VII		N−NaOH (ml)	EtOH (ml)	Reaction condition		I'						
	Prep. No.	mmol			Temp. (°C)	Time (hr.)	R^1	R^2	R^3	R^4	A	position of HO_2C-A-O	Yield (%)
42	66	1.5	3.3	4	25	0.5	$-(CH_2)_5-$		II	5-OH 8-Cl	CH_2	7	90
43	69	1.05	1.2	4	25	1	$-(CH_2)_5-$		II	5-OMe 8-NO_2	CH_2	7	98
44	71	0.397	0.48	2	25	0.5	$-(CH_2)_5-$		II	5-OH 8-SO_2NH_2	CH_2	7	74
45	72	0.465	0.56	2.3	25	0.5	$-(CH_2)_5-$		II	5-OH 8-SO_2NHMe	CH_2	7	95
46	73	0.52	0.62	2.3	25	0.5	$-(CH_2)_5-$		II	5-OH 8-SO_2NMe_2	CH_2	7	91
47	74	2.06	4.5	6	25	0.5	$-(CH_2)_5-$		II	7-OMe	CH_2	5	95

a) Natrium salt

Table 10

Compd. of Ex. No.	M.p. °C (recrystallized)	Molecular formula	Elemental analysis (found) C	H	Cℓ	^{1}H-NMR DMSO-d_6 δ ppm (J Hz)
1	148-149 ether-hexane	$C_{16}H_{16}O_5$	66.19 (66.03)	6.25 (6.35)		7.23(1H, dd, J=9.0 and 2.0), 7.16(1H, d, J=2.0), 6.99(1H, d, J=9.0), 4.67(2H, s), 2.74(2H, s), 2.1-1.1(10H, m)
2	165-166 ether	$C_{16}H_{16}O_5$	66.19 (66.12)	6.25 (6.29)		7.67(1H, d, J=9.0), 6.60(1H, dd, J=9.0 and 2.0), 6.49(1H, d, J=2.0), 4.78(2H, s), 2.69(2H, s), 2.0-1.2(10H, m)
3	139-140 ether	$C_{16}H_{16}O_6$	65.85 (65.76)	4.91 (5.51)		acetone-d_6 11.85(1H, s), 7.6-7.2(5H, m), 6.18(1H, d, J=2.0), 5.94(1H, d, J=2.0), 4.75(2H, s), 3.41(1H, d, J=16.5), 3.18(1H, d, J=16.5), 1.72(3H, s)
4	175-177 ethanol	$C_{15}H_{16}O_6$	61.64 (61.62)	5.52 (5.57)		12.03(1H, s), 6.01(2H, s), 4.75(2H, s), 2.91(2H, s), 2.1-1.5(8H, m)
5	163-164 ether-hexane	$C_{16}H_{16}O_6$	62.74 (62.74)	5.92 (5.95)		acetone-d_6 12.0(1H, s), 6.05(1H, d, J=2.2), 6.97(1H, d, J=2.2), 4.77(2H, s), 2.71(2H, s), 2.2-1.2(10H, m)
6	92-93 ethanol	$C_{16}H_{20}O_6$ $2H_2O$	54.00 (54.34)	6.04 (6.11)		6.11(1H, d, J=2.0), 6.01(1H, d, J=2.0), 4.73(2H, s), 4.70(2H, s), 2.60(2H, s), 2.0-1.0(10H, m)
7	151-152 ethanol	$C_{17}H_{20}O_5$	67.09 (67.05)	6.62 (6.70)		6.42(1H, d, J=2.0), 6.37(1H, d, J=2.0), 4.75(2H, s), 2.63(2H, s), 2.50(3H, s), 2.0-1.2(10H, m)
8	210-211 ethanol	$C_{17}H_{20}O_6$	63.74 (63.70)	6.29 (6.28)		acetone-d_6 12.07(1H, s), 5.99(1H, s), 4.77(2H, s), 2.70(2H, s), 2.2-1.2(13H, s and m)
9	172-173 ethyl acetate-hexane	$C_{16}H_{17}C\ell O_5$	59.17 (59.14)	5.28 (5.23)	10.92 (10.75)	6.66(1H, d, J=2.4), 6.53(1H, d, J=2.4), 4.82(2H, s), 2.73(2H, s), 1.9-1.1(10H, m)
10	253-254 ethanol	$C_{16}H_{16}C\ell_2O_5$	53.50 (53.29)	4.49 (4.56)	19.74 (19.84)	13.3(1H, bs), 6.75(1H, s), 4.98(2H, s), 2.77(2H, s), 1.9-1.15(10H, m)
11	215-217 ether-hexane	$C_{16}H_{16}C\ell_2O_5$	53.50 (53.66)	4.49 (4.55)	19.74 (19.76)	6.86(1H, s), 4.98(2H, s), 2.80(2H, s), 1.95-1.1(10H, m)
12	232-233 ethyl acetate	$C_{11}H_{10}O_6$	55.47 (55.24)	4.23 (4.14)	10.92 (10.75)	13-12(1H, b), 12.1(1H, s), 6.02(2H, s), 4.73(2H, s), 4.46(2H, t, J=6.5), 2.79(2H, t, J=6.5)
13	234-235 acetone	$C_{11}H_{10}O_5$	59.46 (59.15)	4.54 (4.86)		7.68(1H, d, J=9.0), 6.63(1H, dd, J=9.0 and 2.0), 6.48(1H, d, J=2.0), 4.74(2H, s), 4.49(2H, t, J=7.0), 2.69(2H, t, J=7.0)

Table 10 (continued)

Compd. of Ex. No.	M.p. °C (recrystallized)	Molecular formula	Elemental analysis C	Elemental analysis H	^{1}H-NMR DMSO-d_6 δ ppm (J Hz)
14	189-190 ethyl acetate	$C_{13}H_{14}O_5$	62.39 (62.35)	5.64 (5.68)	7.65(1H, d, J=9.0), 6.58(1H, dd, J=9.0 and 2.0), 6.43(1H, d, J=2.0), 4.73(2H, s), 2.19(2H, s), 1.38(6H, s)
15	207-208 ethanol	$C_{12}H_{12}O_5$	61.01 (60.81)	5.12 (5.18)	7.68(1H, d, J=9.0), 6.60(1H, dd, J=9.0 and 2.0), 6.47(1H, d, J=2.0), 4.75(2H, s), 4.60(1H, m), 2.7-2.45(2H, m), 1.42(3H, d, J=7.0)
16	192-193 ethanol	$C_{17}H_{14}O_5$	68.45 (68.15)	4.73 (4.78)	7.77(1H, d, J=9.0), 7.7-7.5(5H, m), 6.70(1H, dd, J=9.0 and 2.0), 6.59(1H, d, J=2.0), 5.65(1H, dd, J=12.0 and 3.0), 4.80(2H, s), 3.70(1H, dd, J=16.5 and 12.0), 2.75(1H, dd, J=16.5 and 3.0)
17	202-203 ether	$C_{13}H_{14}O_6$	58.64 (58.55)	5.30 (5.43)	12.07(1H, s), 6.00(2H, s), 4.74(2H, s), 2.82(2H, s), 1.40(6H, s)
18	210-211 ethanol	$C_{16}H_{20}O_6$	59.34 (59.10)	5.53 (5.57)	acetone-d_6 7.53(1H, d, J=9.0), 6.71(1H, d, J=9.0), 4.89(2H, s), 4.74(2H, s), 2.71(2H, s), 2.1-1.2(10H, m)
19	168-169 ether-hexane	$C_{16}H_{18}O_6$	62.74 (62.41)	5.92 (5.90)	acetone-d_6 7.49(1H, d, J=9.0), 6.53(1H, d, J=9.0), 4.80(2H, s), 2.68(2H, s), 2.0-1.3(10H, m)
20	192-193 ethanol	$C_{16}H_{18}O_6$	62.74 (62.59)	5.92 (5.92)	6.18(1H, d, J=2.0), 6.02(1H, d, J=2.0), 4.75(2H, s), 3.77(3H, s) 2.67(2H, s), 2.0-1.4(8H, m)
21	188-189 ethyl acetate	$C_{17}H_{20}O_6$	63.74 (63.63)	6.29 (6.35)	6.15(1H, d, J=2.0), 6.05(1H, d, J=2.0), 4.74(2H, s), 3.73(3H, s), 2.55(2H, s), 2.0-1.2(10H, m)
22	175-176 ethyl acetate	$C_{16}H_{22}O_6$	64.66 (64.39)	6.63 (6.68)	acetone-d_6 6.16(1H, d, J=2.0), 6.08(1H, d, J=2.0), 4.73(2H, s), 4.04(2H, q, J=7.0), 2.53(2H, s), 2.0-1.2(13H, m)
23	192-193 ethanol	$C_{23}H_{24}O_6$	69.68 (69.50)	6.10 (6.15)	acetone-d_6 7.70-7.25(5H, m), 6.30(1H, d, J=2.0), 6.13(1H, d, J=2.0), 5.17(2H, s), 4.73(2H, s), 2.60(2H, s), 2.1-1.2(10H, m)
24	150-151 ether	$C_{16}H_{24}O_6$	65.50 (65.50)	6.94 (7.04)	acetone-d_6 6.18(1H, d, J=2.0), 6.08(1H, d, J=2.0), 4.72(2H, s), 4.58(1H, m), 2.53(2H, s), 2.0-1.1(m), 1.32(d, J=7.0)(16H)

Table 10 (continued)

Compd. of Ex. No.	M.p. ℃ (recrystallized)	Molecular formula	Elemental analysis C	Elemental analysis H	^{1}H-NMR DMSO-d_6 δ ppm (J Hz)
25	177-178 ethyl acetate	$C_{18}H_{22}O_6$	65.89 (65.73)	6.40 (6.32)	13.11(1H, b), 6.20-5.95(3H, m), 5.61(1H, bd, J=17.2), 5.24(1H, bd, J=10.6), 4.74(2H, s), 4.54(2H, bs), 2.56(2H, s), 1.95-1.10(10H, m)
26	174 ethyl acetate	$C_{25}H_{28}O_7$	68.17 (67.95)	6.41 (6.36)	7.37-7.30(5H, m), 6.18(1H, d, J=2.2), 6.07(1H, d, J=2.2), 4.75(2H, s), 4.65(2H, s), 4.13(2H, bt), 3.77(2H, bt), 2.58(2H, s), 1.9-1.2(10H, m)
27	120-122 ether	$C_{18}H_{22}O_7$	61.71 (61.67)	6.33 (6.39)	6.18(1H, d, J=2.0), 6.07(1H, d, J=2.0), 4.76(2H, s), 3.99(2H, t, J=5.0), 3.70(2H, t, J=5.0), 3.45(1H, b), 2.57(2H, s), 1.9-1.2(10H, m)
28	191-193 acetone-hexane	$C_{18}H_{22}O_6$	64.66 (64.48)	6.63 (6.67)	acetone-d_6 6.15(1H, d, J=2.0), 6.03(1H, d, J=2.0), 4.91(1H, q, J=6.5), 3.79(3H, s), 2.53(2H, s), 1.58(3H, d, J=6.5), 2.1-1.1(10H, m)
29	167-169 acetone- ethyl acetate-ether	$C_{18}H_{24}O_6$	65.50 (65.49)	6.94 (7.00)	acetone-d_6 6.14(2H, s), 4.10(2H, t, J=6.4), 3.80(3H, s), 2.53(2H, s), 2.47(2H, t, J=6.3), 2.63-1.15(12H, m)
30	111-112 ether-hexane	$C_{18}H_{22}O_6$ 1/2H_2O	62.96 (62.87)	6.75 (6.63)	$CDCl_3$ 9.5(1H, bs), 6.14(1H, d, J=2.0), 6.03(1H, d, J=2.0), 4.70(2H, s), 3.83(3H, s), 2.55(1H, q, J=7.0), 2.1-1.2(10H, m), 1.12(3H, d, J=7.0)
31	203-204 ethyl acetate	$C_{18}H_{22}O_6$	64.66 (64.37)	6.63 (6.62)	6.17(1H, s), 4.80(2H, s), 3.74(3H, s), 2.53(2H, s), 2.03(3H, s), 2.0-1.2(10H, m)
32	230-232 (decomposition) ethanol	$C_{12}H_{12}O_6$	57.14 (57.16)	4.79 (4.80)	6.19(1H, d, J=2.2), 6.07(1H, d, J=2.2), 4.75(2H, s), 4.39(2H, t, J=6.4), 3.76(3H, s), 2.59(2H, t, J=6.4)
33	220-222 ethyl acetate	$C_{14}H_{10}O_6$	59.99 (59.82)	5.75 (5.75)	6.17(1H, d, J=2.0), 6.02(1H, d, J=2.0), 4.75(2H, s), 3.77(3H, s), 2.58(2H, s), 1.34(6H, s)
34	174-175 ether	$C_{17}H_{20}O_6$	63.74 (63.59)	6.29 (6.30)	acetone-d_6 7.49(1H, d, J=9.0), 6.65(1H, d, J=9.0), 4.83(2H, s), 3.90(3H, s), 2.67(2H, s), 2.0-1.2(10H, m)

Table 10 (continued)

Compd. of Ex. No.	M.p. ℃ (recrystallized)	Molecular formula	Elemental analysis (found) C	H	Cℓ	Na	^{1}H-NMR DMSO-d_6 δ ppm(J Hz)
35	269-270 ethanol	$C_{17}H_{18}O_6Na$	59.64 (59.59)	5.59 (5.67)		6.72 (6.89)	acetone-d_6 7.55(1H, d, J=9.0), 6.75(1H, d, J=9.0), 4.64(2H, s), 3.95(3H, s), 2.68(2H, s), 2.1-1.2(10H, m)
36	221-222 ethanol	$C_{16}H_{17}ClO_6$	59.17 (59.30)	5.28 (5.33)	10.92, (11.06)		7.67(1H, s), 6.70(1H, s), 4.93(2H, s), 2.73(2H, s), 2.0-1.2(10H, m)
37	150-151 ether-hexane	$C_{17}H_{18}Cl_2O_6$	52.46 (52.34)	4.66 (4.71)	18.22 (18.46)		acetone-d_6 4.77(2H, s), 3.82(3H, s), 2.74(2H, s), 2.1-1.3(10H, m)
38	196-197 ethanol	$C_{17}H_{19}ClO_6$	57.55 (57.52)	5.40 (5.36)	9.99 (9.83)		acetone-d_6 6.49(1H, s), 4.90(2H, s), 3.82(3H, s), 2.15(2H, s), 2.1-1.3(10H, m)
39	201-202 ethanol	$C_{17}H_{19}ClO_6$	57.55 (57.30)	5.40 (5.56)	9.99 (10.08)		acetone-d_6 6.38(1H, s), 4.94(2H, s), 3.83(3H, s), 2.60(2H, s), 2.1-1.3(10H, m)
40	154-155 ether-hexane	$C_{16}H_{18}Cl_2O_6$	51.22 (51.08)	4.30 (4.36)	18.90 (19.14)		acetone-d_6 12.47(1H, b), 8-6(1H, b), 4.78(2H, s), 2.90(2H, s), 2.2-1.2(10H, m)
41	213-214 ethanol	$C_{16}H_{17}ClO_6$	56.40 (56.32)	5.03 (5.02)	10.40 (10.62)		acetone-d_6 12.5(1H, s), 6.23(1H, s), 6.1-5.0(1H, b), 4.90(2H, s), 2.77(2H, s), 2.1-1.2(10H, m)
42	195-196 ethanol	$C_{16}H_{17}ClO_6$	56.40 (56.19)	5.03 (5.01)	10.40 (10.54)		acetone-d_6 12.07(1H, s), 6.14(1H, s), 6.0-5.0(1H, b), 4.88(2H, s), 2.78(2H, s), 2.1-1.2(10H, m)

Table 10 (continued)

Compd. of Ex. No.	M.p. ℃ (recrystallized)	Molecular formula	Elemental analysis (found) C	H	Cℓ	S	^{1}H-NMR DMSO-d_6 δ ppm(J Hz)
43	243-245 ethanol	$C_{17}H_{19}NO_6$	55.89 (56.18)	5.24 (5.56)	3.83 (3.63)		6.44(1H, s), 5.01(2H, s), 3.87(3H, s), 2.68(2H, s), 2.1-1.2(10H, m)
44	238-240 (decomposition) ethanol-water	$C_{17}H_{21}NO_6S$ 1/2H_2O	51.12 (49.99)	5.30 (5.43)	3.51 (3.43)	8.03 7.85	13.6(1H, b), 7.11(2H, s), 6.34(1H, s), 4.99(2H, s), 3.86(3H, s), 2.59(2H, s), 2.0-1.1(10H, m)
45	272-274 (decomposition) ethanol	$C_{18}H_{23}NO_6S$ 1/2H_2O	51.18 (51.44)	5.72 (5.61)	3.31 (3.24)	7.59 (7.15)	13.6(1H, s), 6.33(1H, s), 5.02(2H, s), 6.83(1H, q, J=5.4), 3.86(3H, s), 2.62(2H, s), 2.50(3H, d, J=5.4), 2.0-1.1(10H, m)
46	238-239 ethanol	$C_{18}H_{25}NO_6S$	53.39 (53.18)	5.89 (5.73)	3.28 (3.22)	7.50 (7.22)	13.3(1H, s), 6.21(1H, s), 5.03(2H, s), 3.82(3H, s), 2.79(6H, s), 2.61(2H, s), 1.95-1.13(10H, m)
47	150-151 ether	$C_{17}H_{20}O_6$	63.74 (63.70)	6.29 (6.27)			acetone-d_6 6.28(2H, s), 4.76(2H, s), 3.89(3H, s), 2.68(2H, s), 2.1-1.2(10H, m)

Example 48

2-{(5-Methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)amino}acetic acid

A mixture of (4′-amino-2′,6′-dimethoxyphenyl) ethanone (prepared in Preparation 76) (1.185 g, 6.08 mmol), dry dichloromethane (30 ml), triethylamine (0.55 g, 5.5 mmol, and trifluoroacetic acid anhydride (1.15 g, 5.48 mmol)) is stirred for 1.5 hours under ice-cooling, which is followed by the addition of dichloromethane. The mixture is washed with dilute hydrochloric acid and then water, dried, and the solvent is removed by distillation. The residue is placed on a silica gel column and eluted with a mixtue of dichloromethane and ethyl acetate (1:1) to yield a crude product. Recrystallization from a mixture of diethyl ether and hexane gives (4′-trifluoroacetylamino-2′,6′-dimethoxyphenyl)ethanone as a crystalline solid (1.67 g, yield 85%, m.p. = 172 - 173 °C).

Elemental analysis (for $C_{12}H_{12}F_3NO_4$)			
Calcd.:	C, 49.49;	H, 4.15;	N, 4.81
Found:	C, 49.51;	H, 4.19;	N, 5.05

^{1}H-NMR ($CDCl_3$) δppm: 8.42(1H,b), 6.83(2H,s), 3.78(6H,s), 2.46(3H,s).

A mixture of above (4′-trifluoroacetylamino-2′,6′-dimethoxyphenyl)ethanone (1.73 g, 5.95 mmol), anhydrous DMF (60 ml), anhydrous potassium carbonate (0.50 g, 3.62 mmol), and methyl bromoacetate (0.55 g, 3.74 mmol) is heated at 70 °C for 45 minutes with stirring. The mixture is diluted with water and extracted with ethyl acetate. The ethyl acetate layer is washed with water, dried, and the solvent is removed by distillation. The residue is placed on a silica gel column and eluted with a mixture of dichloromethane and ethyl acetate (15:1) to yield a crude product. Recrystallization from hexane gives methyl (4′-acetyl-3′,5′-dimethoxyphenyl-N-trifluoroacetylamino)acetate (1.26 g, yield 91%, m.p. = 108 - 109 °C).

^{1}H-NMR ($CDCl_3$) δppm: 6.60(2H,s), 4.37(2H,s), 3.80(9H,s), 2.47(3H,s).

To a solution of above methyl (4′-acetyl-3′,5′-dimethoxyphenyl-N -trifluoroacetylamino)acetate (1.2 g, 3.36 mmol) in anhydrous dichloromethane (50 ml) is added dropwise 2 M boron trichloride in dichloromethane (3.89 ml, 7.78 mmol) at -30 °C. After 1.5 hours stirring at room temperature, ice-cold water is added to the mixture. The mixture is then extracted with dichloromethane. The extract is washed with water, dried, and the solvent is removed by distillation. The residue is placed on a silica gel column and eluted with a mixture of dichloromethane and ethyl acetate (20:1) to obtain a crystalline product (1.04 g, yield 90%, m.p. = 79 - 80 °C). The crystalline product (0.95 g) is dissolved in absolute methanol (40 ml), and 0.2 N sodium methylate solution in methanol (10.65 ml) is added dropwise to it at 0 °C. After 20 minutes stirring, the solvent is removed by distillation. The residue is placed on a silica gel column and eluted with a mixture of dichloromethane and ethyl acetate (20:1) to obtain methyl (4′-acetyl-3′-hydroxy-5′-methoxyphenylamino)-acetate (0.388 g, yield 56%, m.p. = 114 - 115 °C).

Elemental analysis (for $C_{12}H_{15}NO_5$)			
Calcd.:	C, 56.91;	H, 5.97;	N, 5.53
Found:	C, 56.92;	H, 5.95;	N, 5.73

^{1}H-NMR ($CDCl_3$) δppm: 14.2(1H,b), 5.65(1H,d,J = 1.5), 5.55(1H,d,J = 1.5), 3.90(2H,s), 3.81(6H,s), 2.55(3H,s).

A mixture of methyl (4′-acetyl-3′-hydroxy-5′-methoxyphenylamino)acetate obtained above (0.388 g, 1.53 mmol), absolute ethanol (30 ml), and cyclohexanonepyrrolidine enamine (0.462 g, 3.02 mmol) is heated to reflux for 2 hours under argon gas, and the solvent is removed. The residue is dissolved in ethyl acetate. The solution is washed with diluted HCl and then water, dried, and the solvent is removed. The residue is placed on a silica gel column and eluted with a mixture of dichloromethane and ethyl acetate (1:1). The starting material (0.06 g, 15.5%) is recovered from the earlier fractions. From the succeeding fractions,

methyl 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2 H -1-benzopyran-2,1′-cyclohexan]-7-yl)amino}acetate is obtained as a crystalline solid (0.481 g, 82%, m.p. = 168 - 169 °C).

Elemental analysis (for $C_{18}H_{23}NO_5$)			
Calcd.:	C, 64.85;	H, 6.95;	N, 4.20
Found:	C, 64.57;	H, 7.00;	N, 4.53

^{1}H-NMR ($CDCl_3$) δppm: 5.71(1H,d,J = 2.2), 5.69(1H,d,J = 2.2), 5.7 - 4.6(1H,b), 3.95(2H,s), 3.86(3H,s), 3.82-(3H,s), 2.59(2H,s), 2.1 - 1.2(10H,m).

A mixture of methyl 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)-amino}acetate obtained above (0.394 g, 1.18 mmol), 1 N sodium hydroxide (1.19 ml, 1.19 mmol), and ethanol (10 ml) is stirred at room temperature for one hour. Ethanol is distilled under reduced pressure, and the residue is dissolved in water. The aqueous solution is washed with ethyl acetate, and filtered to remove insoluble substances. The filtrate is adjusted to pH 5 - 6 with dilute HCl. The resulting crystalline precipitate is separated by filtration, washed with water and dried to yield the title compound as a crystalline solid (0.351 g, 93%, m.p. = 112 -113 °C).

Elemental analysis (for $C_{17}H_{21}NO_5$)			
Calcd.:	C, 63.94;	H, 6.63;	N, 4.39
Found:	C, 63.82;	H, 6.60;	N, 4.23

^{1}H-NMR (d_6-acetone) δppm: 5.98(1H,d,J = 2.2), 5.95(1H,b), 5.79(1H,d,J = 2.2), 4.03(2H,d,J = 5.2), 3.74(3H,s), 2.45(2H,s), 2.1 - 1.2(10H,m).

Example 49

2-{(5-Hydroxy-3,4-dihydro-4-oxospiro[2 H -1-benzothiine-2,1′-cyclohexan]-7yl)oxy}acetic acid

(1) A mixture of 5,7-dihydroxy-spiro[2H -1-benzothiine-2,1′-cyclohexan]-4(3H)-one (prepared in Preparation 79) (0.47 g, 1.78 mmol), ethyl bromoacetate (0.297 g, 1.78 mmol), anhydrous potassium carbonate (0.368 g, 2.67 mmol), and dry acetonitrile (5 ml) is stirred overnight at room temperature. The mixture is stirred at 35 °C for additional 5 hours. The reaction mixture is filtered to remove inorganic materials. The solvent is removed by distillation from the filtrate. The residue is placed on a silica gel column and eluted with a mixture of dichloromethane and ethyl acetate (9:1) to obtain ethyl 2-{(5-hydroxy-3,4-dihydro-4-oxospiro[2H -1-benzothiine-2,1′-cyclohexan]-7-yl)oxy}acetate as a crystalline solid (0.57 g, 91.5%). Recrystallization from diethyl ether gives a product having a melting point of 87 - 88 °C.

Elemental analysis (for $C_{18}H_{22}O_5S$)			
Calcd.:	C, 61.69;	H, 6.33;	S, 9.15
Found:	C, 61.73;	H, 6.45;	S, 8.95

^{1}H-NMR ($CDCl_3$) δppm: 13.05(1H,s), 6.36(1H,d,J = 2.4), 6.09(1H,d,J = 2.4), 4.61(2H,s), 4.28(2H,q,J = 7), 2.90(2H,s), 2.0 - 1.2(10H,m), 1.30(3H,t,J = 7).

(2) A mixture of the crystalline solid (0.11 g, 0.314 mmol) obtained above (1), 1 N-sodium hydroxide (0.76 ml, 0.76 mmol), and ethanol (1 ml) is stirred at room temperature for 2 hours. The mixture is made acidic with dilute HCl. The resulting crystalline precipitates are separated by filtration, washed with water, dried and recrystallized from diethyl ether to yield the title compound as a crystalline solid (0.092 g, 90%, m.p. = 189 -190 °C).

Elemental analysis (for $C_{16}H_{18}O_5S$)			
Calcd.:	C, 59.61;	H, 5.63;	S, 9.94
Found:	C, 59.39;	H, 5.85;	S, 9.82

^{1}H-NMR (d_6-DMSO) δppm: 13.03(1H,s), 6.42(1H,d,J = 2.4), 6.19(1H,d,J = 2.4), 4.78(2H,s), 2.98(2H,s), 1.9 - 1.1(10H,m).

Example 50

2-{(5-Methoxy-3,4-dihydro-4-oxospiro[2H -1-benzothiin-2,1′-cyclohexan]-7-yl)oxy}acetic acid

A mixture of ethyl 2-{(5-hydroxy-3,4-dihydro-4-oxospiro[2H -1-benzothiin-2,1′-cyclohexan-7-yl)-oxy}acetate (prepared in Example 49 (1)) (0.129 g, 0.369 mmol), methyl iodide (0.078 g, 0.56 mmol), anhydrous potassium carbonate (0.102 g, 0.74 mmol), and dry DMF (1 ml) is stirred overnight at room temperature and the solvent is removed by distillation. The residue is dissolved in diethyl ether. The solution is washed with saturated brine, dried and concentrated. The residue is placed on a silica gel column and eluted with a mixtue of dichloromethane and ethyl acetate (9:1) to obtain a product as a crystalline solid (0.118 g, 88%). Recrystallization from ethanol gives a product having a melting point of 121 - 122 °C).

Elemental analysis (for $C_{19}H_{24}O_5S$)			
Calcd.:	C, 62.62;	H, 6.64;	S, 8.80
Found:	C, 62.40;	H, 6.59;	S, 8.53

^{1}H-NMR ($CDCl_3$) δppm: 6.29(2H,s), 4.62(2H,s), 4.26(2H,q,J = 7), 3.87(3H,s), 2.86(2H,s), 2.2 - 1.2(10H,m), 1.30(3H,t,J = 7).

A mixture of the above crystalline solid (0.085 g, 0.23 mmol), 1 N-sodium hydroxide (0.28 ml, 0.28 mmol), and ethanol (2 ml) is stirred at room temperature for 0.5 hours. The mixture is made acidic with dilute HCl and distilled under reduced pressure to remove ethanol. The residue is extracted with a mixture of diethyl ether and dichloromethane (1:1). The organic layer is washed with saturated brine, dried, and the solvent is removed. The crystalline residue is washed with diethyl ether and recrystallized from ethanol to yield the title compound (0.070 g, 89.4%, m.p. = 195 - 196 °C).

Elemental analysis (for $C_{17}H_{20}O_5S$)			
Calcd.:	C, 60.70;	H, 5.99;	S, 9.53
Found:	C, 60.59;	H, 5.96;	S, 9.29

^{1}H-NMR (d_6-DMSO) δppm: 13.14(1H,s), 6.40(1H,d,J = 2.2), 6.38(1H,d,J = 2.2), 4.80(2H,s), 3.77(3H,s), 2.80-(2H,s), 1.9 - 1.1(10H,m).

Example 51

2-{(5-Hydroxy-4-oxospiro[1,2,3,4-tetrahydroquinoline-2,1′-cyclohexan]-7-yl)oxy}acetic acid

(1) A mixture of 5,7-dihydroxy spiro[1,2,3,4-tetrahydroquinoline-2,1′-cyclohexan]-4-one (prepared in Preparation 81) (0.247 g, 1.0 mmol), ethyl bromoacetate (0.184 g, 1.10 mmol), anhydrous potassium carbonate (0.207 g, 1.5 mmol), and dry acetonitrile (4 ml) is stirred at room temperature for 4 hours. The

solvent is removed under reduced pressure and the residue is extracted with ethyl acetate and water. The ethyl acetate layer is separated, washed with water, dried, and the solvent is removed. The residue is placed on a silica gel column and eluted with a mixture of acetone and dichloromethane (1:10) to obtain a crude product. Recrystallization from a mixture of diethyl ether and hexane gives ethyl 2-{(5-hydroxy-4-oxospiro[1,2,3,4-tetrahydroquinoline-2,1′-cyclohexan]-7-yl)oxy}acetate (0.265 g, 79%, m.p. = 134 - 135 °C).

Elemental analysis (for $C_{18}H_{23}NO_5$)			
Calcd.:	C, 64.85;	H, 6.95;	N, 4.20
Found:	C, 64.52;	H, 7.01;	N, 4.15

^{1}H-NMR ($CDCl_3$) δppm: 12.47(1H,s), 5.70(1H,d,J = 2.4), 5.64(1H,d,J = 2.4), 4.58(2H,s), 4.45(1H,b), 4.28-(2H,q,J = 7), 2.60(2H,s), 1.9 - 1.2(10H,m), 1.31(3H,t,J = 7).

(2) A mixture of the product obtained in (1) (0.103 g, 0.31 mmol), 0.2 N sodium hydroxide (1.85 ml, 0.37 mmol), and ethanol (2 ml) is stirred at room temperature for 0.75 hours. The mixture is made acidic with dilute HCl and distilled under reduced pressure to remove ethanol. The residue is extracted with ethyl acetate. The organic layer is separated, washed with saturated brine, dried, and the solvent is removed to obtain crystalline residue. The residue is washed with diethyl ether, and recrystallized from ether to obtain the title compound (0.090 g, 95%, m.p. = 177 - 178 °C).

Elemental analysis (for $C_{16}H_{19}NO_5 \cdot 1/2H_2O$)			
Calcd.:	C, 61.14;	H, 6.41;	N, 4.45
Found:	C, 61.36;	H, 6.50;	S, 4.33

^{1}H-NMR (d_6-DMSO) δppm: 13.10(1H,b), 12.46(1H,s), 6.87(1H,bs), 5.83(1H,d,J = 2.2), 5.52(1H,d,J = 2.2), 4.62-(2H,s), 2.51(2H,s), 1.80 - 1.20(10H,m).

Example 52

2{(5-methoxy-4-oxospiro[1,2,3,4-tetrahydroquinoline-2,1′-cyclohexan]-7-yl)oxy}acetic acid

(1) A mixture of ethyl 2-{(5-hydroxy-4-oxospiro[1,2,3,4-tetrahydroquinoline-2,1′-cyclohexan]7-yl)oxy)-acetate (prepared in Example 51 (1)) (0.15 g, 0.45 mmol), methyl iodide (0.071 g, 0.50 mmol), anhydrous potassium carbonate (0.094 g, 0.68 mmol), and dry DMF (4 ml) is stirred at 40 °C for 9 hours. After the addition of methyl iodide (0.14 g, 1.0 mmol), the stirring is continued for an additional 4 hours. The solvent is removed by distillation and the residue is dissolved in ethyl acetate. The solution is washed with saturated brine, dried, and the solvent is removed. The residue is placed on a silica gel column and eluted with a mixture of ethyl acetate and dichloromethane (1:10). The earlier fractions containing oily materials are discarded. From the succeeding fractions, the desired product is obtained as a crystalline solid (0.067 g, 43%, m.p. = 158 - 159 °C).

^{1}H-NMR ($CDCl_3$) δppm: 5.83(1H,d,J = 2.4), 5.62(1H,d,J = 2.4), 4.58(2H,s), 4.29(2H,q,J = 7), 3.84(3H,s), 2.57(2H,s), 2.9 - 1.2(10H,m), 1.31(3H,t,J = 7).

(2) A mixture of the above crystalline solid (0.060 g, 0.173 mmol), 0.2 N sodium hydroxide (1 ml, 0.2 mmol), and ethanol (1 ml) is stirred at room temperature for 1.75 hours. The mixture is made acidic with dilute HCl. Ethanol is removed under reduced pressure to yield a crystalline residue. The residue is dissolved in acetone and the mixture is filtered to remove insoluble materials. The filtrate is distilled under reduced pressure. The residue is recrystallized from a mixture of acetone and diethyl ether to yield the title compound as a crystalline solid (0.031 g, 56%, m.p. = 241 - 242 °C).

Elemental analysis (for $C_{17}H_{21}NO_5 \cdot 1/2H_2O$)			
Calcd.:	C, 58.94;	H, 6.98;	N, 4.04
Found:	C, 58.64;	H, 6.75;	S, 4.04

^{1}H-NMR (d_6-DMSO) δppm: 13.10(1H,b), 6.65(1H,bs), 5.94(1H,d,J = 2.2), 5.69(1H,d,J = 2.2), 4.61(2H,s), 3.66-(3H,s), 2.33(2H,s), 1.80 - 1.20(10H,m).

Example 53

{(5-Methoxy-4-chlorospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}acetic acid

{(5-Methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy}acetic acid (prepared in Example 21) (0.29 g, 0.91 mmol) is reacted with an excess of diazomethane in diethyl ether. The mixture is distilled to remove diazomethane and ether. To the residue is added oxalyl chloride (0.463 g, 3.65 mmol) and dry benzene (10 ml), and the mixture is heated to reflux for 3.5 hours. The solvent is removed under reduced pressure. The residue is placed on a silica gel column and eluted with a mixture of ethyl acetate and hexane (1:2) to obtain methyl {(5-methoxy-4-chlorospiro[2H -1-benzopyran-2,1′-cyclohexan-7-yl)-oxy}acetate as a crystalline solid (0.30 g, 93%).

A mixture of the obtained ester (0.30 g, 0.85 mmol), 1 N sodium hydroxide (1 ml, 1.0 mmol), and ethanol (2 ml) is stirred at room temperature for 0.5 hours. The reaction mixture is made acidic with 1 N HCl and distilled under reduced pressure at room temperature to remove ethanol. The residue is extracted with diethyl ether. The extract is washed with saturated brine, dried, and the solvent is removed under reduced pressure. The residue is treated with diethyl ether and recrystallized from 80% ethanol to obtain the title compound (0.185 g, 64.5%, m.p. = 132 - 133 °C).

Elemental analysis (for $C_{17}H_{19}ClO_5$)			
Calcd.:	C, 60.27;	H, 5.65;	Cl. 10.46
Found:	C, 60.13;	H, 5.75;	Cl, 10.18

^{1}H-NMR (d_6-DMSO) δppm: 13.05(1H,b), 6.22(1H,d,J = 2.4), 6.12(1H,d,J = 2.4), 5.75(1H,s), 4.70(2H,s), 3.76-(3H,s), 1.85- 1.1(10H,m).

Example 54

{(5-Methoxy-3,4-dihydrodispiro[2H -1-benzopyran-2,1′-cyclohexan-4,2″-[1,3]dithiolan]-7-yl)oxy}acetic acid

A mixture of ethyl {(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan]-7-yl)oxy)-acetate (prepared in Preparation 49) (0.5 g, 1.44 mmol), ethanedithiol (0.149 g, 1.59 mmol), dry benzene (10 ml), and p -toluenesulfonic acid (0.013 g, 0.076 mmol) is heated to reflux for 12 hours under conditions for azeotropic dehydration. The solvent is removed under reduced pressure. The residue is applied to a silica gel column and eluted with a mixture of ethyl acetate and dichloromethane (1:9). The eluate is applied to a Lober column and eluted with a mixture of ethyl acetate and hexane (1:2) to obtain ethyl ((5-methoxy-3,4-dihydrodispiro[2H -1-benzopyran-2,1′-cyclohexan4,2″-[1,3]dithiolan]-7-yl)oxy}acetate as an oil (0.50 g, 82.1%). A mixture of the ester (0.49 g, 1.16 mmol), 1 N sodium hydroxide (1.27 ml, 1.27 mmol), and ethanol (5 ml) is stirred at room temperature for 0.5 hours. The reaction mixture is made acidic with 1 N HCl and distilled under reduced pressure at room temperature to remove ethanol. The residue is extracted with diethyl ether. The extract is washed with saturated brine, dried, and the solvent is removed under reduced pressure. The residue is treated with a mixture of diethyl ether and hexane to obtain the title compound as

a crystalline solid (0.43 g, 93.7%). Recrystallization from ethyl acetate gives a product having a melting point of 189 - 190 °C.

Elemental analysis (for $C_{19}H_{24}O_5S_2$)			
Calcd.:	C, 57.55;	H, 6.10;	S, 16.17
Found:	C, 57.39;	H, 5.95;	S, 16.46

^{1}H-NMR (d_6-DMSO) δppm: 13.0(1H,b), 6.15(1H,d,J = 2.4), 5.88(1H,d,J = 2.4), 4.62(2H,s), 3.77(3H,s), 3.6 - 3.3-(4H,m), 2.55(2H,s), 1.8 - 1.2(10H,m).

Example 55

2-{ N -acetyl-(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan-7-yl)amino}acetic acid

To a solution of 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan-7-y)-amino}acetic acid (prepared in Example 48) (0.204 g, 0.64 mmol) in pyridine (3 ml) is added acetyl chloride (0.126 g, 1.61 mmol) and the mixture is stirred two overnights at room temperature. To the reaction mixture is added ice and dilute hydrochloric acid, and the mixture is extracted with ethyl acetate. The extract is washed with water, dried, and the solvent is removed. The residue is applied to a silica gel column and eluted with a mixture of ethyl acetate, dichloromethane and acetic acid (200:800:1). The eluate is distilled under reduced pressure and the residue is dissolved in ethyl acetate. The solution is washed with water, dried, and the solvent is removed to obtain the title compound as an amorphous substance (0.080 g, 33%).

Elemental analysis (for $C_{19}H_{23}NO_6 \cdot 5/4H_2O$)			
Calcd.:	C, 59.44;	H, 6.69;	N, 3.65
Found:	C, 59.70;	H, 6.42;	N, 3.61

^{1}H-NMR ($CDCl_3$) δppm: 6.56(1H,d,J = 1.6), 6.46(1H,d,J = 1.6), 4.9(1H,b), 4.38(2H,s), 3.90(3H,s), 2.69(2H,s), 2.06(3H,s), 2.1 - 1.2(10H,m).

Example 56

Pivaloyloxymethyl 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan-7-yl)oxy}acetic acid

To a solution of 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan-7-yl)-oxy}acetic acid (prepared in Example 21) (4.0 g, 12.5 mmol) in acetonitrile (30 ml) is added 2 N potassium hydroxide (7.5 ml, 15 mmol) and the mixture is stirred at room temperature for 2 hours. The solvent is removed under reduced pressure. The residue is mixed with ethanol and the mixture is filtered to separate potassium 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan-7-yl)oxy}acetate as a crystalline solid (4.11 g, 92%). To a solution of the crystalline potassium salt (2.0 g, 5.6 mmol) in dry DMF (20 ml) is added 1-iodomethyl pivalate (1.756 g, 7.25 mmol), and the mixture is stirred at room temperature for 3 hours and distilled under reduced pressure. To the residue is added ice-cold water and the mixture is extracted with ethyl acetate. The extract is dried and distilled under reduced pressure. The residue is purified by silica gel column chromatography (eluent : dichloromethane and acetone, 20:1). The eluate is treated with a mixture of diethyl ether and hexane to obtain the title compound as a crystalline solid (2.0 g, 82.6%, m.p. = 110 - 111 °C).

Elemental analysis (for $C_{23}H_{30}O_8$)		
Calcd.:	C, 63.59;	H, 6.96
Found:	C, 63.58;	H, 6.97

^{1}H-NMR ($CDCl_3$) δppm: 6.12(1H,d,J = 2.4), 5.96(1H,d,J = 2.4), 5.86(2H,s), 4.68(2H,s), 3.87(3H,s), 2.62-(2H,s), 2.05 - 1.25(10H,m), 1.22(9H,s).

Example 57

1-(Pivaloyloxy)ethyl 2-{(5-methoxy-3,4-dihydro-4-oxospiro [2H -1-benzopyran-2,1′-cyclohexan-7-yl)-oxy}acetate

To a solution of potassium 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan-7-yl)oxy}acetate (prepared in Example 56) (0.50 g, 1.4 mmol) in dry DMF (5 ml) is added 1-iodoethyl pivalate (0.523 g, 1.68 mmol), and the mixture is stirred at room temperature for 0.5 hours and allowed to stand overnight at 5 °C. The mixture is reacted at room temperature for an additional one hour with stirring. The reaction mixture is then treated in a same manner as Example 56. Recrystallization from a mixture of diethyl ether and hexane gives the title compound as a crystalline solid (0.372 g, 59%, m.p.= 121 - 122 °C).

Elemental analysis (for $C_{24}H_{32}O_8 \cdot 1/4H_2O$)		
Calcd.:	C, 63.63;	H, 7.23
Found:	C, 63.72;	H, 7.10

^{1}H-NMR ($CDCl_3$) δppm: 6.91(1H,q,J = 5.4), 6.09(1H,d,J = 2.4), 5.97(1H,d,J = 2.4), 4.63(2H,s), 3.86(3H,s), 2.61-(2H,s), 2.05- 1.10(10H,m), 1.49(3H,d,J = 5.4), 1.18(9H,s).

Example 58

1-[(2-Cyclohexylacetyl)oxy]ethyl 2-[5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan-7-yl)oxy]acetate

To a solution of potassium 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1′-cyclohexan-7-yl)oxy}acetate (prepared in Example 56) (0.50 g, 1.4 mmol) in dry DMF (5 ml) is added 1-chloroethyl cyclohexyl acetate (0.37 g, 1.81 mmol), and the mixture is stirred at 70 °C for 3 hours. The reaction mixture is treated the same manner as Example 56 to yield the title compound as a thick syrup (0.343 g, 50%).

Elemental analysis (for $C_{27}H_{36}O_8$)		
Calcd.:	C, 66.38;	H, 7.43
Found:	C, 66.32;	H, 7.58

^{1}H-NMR ($CDCl_3$) δppm: 6.92(1H,q,J = 5.4), 6.08(1H,d,J = 2.2), 5.96(1H,d,J = 2.2), 4.60(2H,s), 3.85(3H,s), 2.59-(2H,s), 2.17(2H,d,J = 7.0), 2.00- 0.80(21H,m), 1.50(3H,d,J = 5.4).

Example 59

1-(Methoxycarbonyloxy) ethyl 2-[(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1'-cyclohexan-7-yl)oxy]acetate

To a solution of potassium 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1'-cyclohexan-7-yl)oxy}acetate (prepared in Example 56) (0.50 g, 1.4 mmol) in dry DMF (5 ml) is added 1-chloroethyl methylcarbonate (0.232 g, 1.68 mmol). The mixture is stirred at room temperature for one hour, and then at 70 °C for one hour. The reaction mixture is treated in a same manner as Example 56. Recrystallization from a mixture of diethyl ether and hexane gives the title compound as a crystalline solid (0.234 g, 40%, m.p. = 97 - 98 °C).

Elemental analysis (for $C_{21}H_{26}O_9$)		
Calcd.:	C, 59.71;	H, 6.20
Found:	C, 59.74;	H, 6.17

^{1}H-NMR ($CDCl_3$) δppm: 6.84(1H,q,J = 5.4), 6.08(1H,d,J = 2.3), 5.98(1H,d,J = 2.3), 4.63(2H,s), 3.85(3H,s), 3.79-(3H,s), 2.60(2H,s), 2.00 - 1.20(10H,m), 1.54(3H,d,J = 5.4).

Example 60

Phthalidyl 2-[(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1'-cyclohexan-7-yl)oxy]acetate

To a solution of potassium 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1'-cyclohexan-7-yl)oxy}acetate (prepared in Example 56) (2.18 g, 6.1 mmol) in dry DMF (20 ml) is added phthalidyl bromide (1.684 g, 7.9 mmol) and the mixture is stirred at room temperature for 7.5 hours, and distilled under reduced pressure. To the residue is added ice-cold water and the mixture is extracted with ethyl acetate. The extract is washed with water, dried, and distilled under reduced pressure. The resulting residue is purified by silica gel column chromatography (eluent: dichloromethane and acetone, 20:1) to yield the title compound as a crystalline solid (1.394 g, 51%, m.p. = 119 -120 °C).

Elemental analysis (for $C_{25}H_{24}O_8$)		
Calcd.:	C, 66.37;	H, 5.35
Found:	C, 66.07;	H, 5.52

^{1}H-NMR ($CDCl_3$) δppm: 8.05 - 7.50(5H,m), 6.11(1H,d,J = 2.2), 5.99(1H,d,J = 2.2), 4.75(2H,s), 3.86(3H,s), 2.64(2H,s), 2.10- 1.20(10H,m).

Example 61

1,5-Dihydro-1-{2-[(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1'-cyclohexan-7-yl)oxy]-acetyloxymethyl}-4H-pyrazolo[3,4-d]pyrimidin-4-one

To a mixture of 2-{(5-methoxy-3,4-dihydro-4-oxospiro[2H -1-benzopyran-2,1'-cyclohexan-7-yl)-oxy}acetic acid (prepared in Example 21) (0.960 g, 3.0 mmol), triphenylphosphine (0.944 g, 3.6 mmol), 1,5-dihydro-1-hydroxymethyl-4H-pyrazolo[3,4-d]pyrimidin-4-one [P.C.Bausal, I.H.Pitman, and T.Higuchi,

J.Pharm.Sci., 70, 855, (1981)] (0.548 g, 3.3 mmol) in dry dioxane (20 ml) is added a solution of diethyl azodicarboxylate (0.626 g1 3.6 mmol) in dioxane (10 ml). After 3 days stirring at room temperature, diethyl azodicarboxylate (0.104 g, 0.6 mmol) is added to it and the mixture is stirred for an additional 2 hours. The mixture is distilled under reduced pressure and the residue is purified by silica gel column chromatography (eluent: dichloromethane and methanol, 20:1). Recrystallization from ethyl acetate gives the title compound as a crystalline solid (1.0 g, 70%, m.p. = 139 - 141 °C).

Elemental analysis (for $C_{23}H_{24}N_4O_7 \cdot 1/2H_2O$)			
Calcd.:	C, 57.86;	H, 5.28;	N, 11.73
Found:	C, 57.70;	H, 5.08;	N, 11.84

^{1}H-NMR (d_6-DMSO) δppm: 12.45(1H,s), 8.21(1H,s), 8.18(1H,s), 6.35(2H,s), 6.14(1H,d,J = 2.2), 6.04-(1H,d,J = 2.2), 4.94(2H,s), 3.72(3H,s), 2.56(2H,s), 1.85 - 1.25(10H,m).

The following experiments were conducted to demonstrate the ability of the compounds of the present invention in the acceleration of the excretion of uric acid and inhibition of xanthine oxidase which leads to inhibition of biosynthesis of uric acid.

Experiment 1

Accelerated uric acid clearance in rats caused by administration of compound (I).

a) Method

Nine-week-old male rats were employed for the test. As a pre-treatment for measuring uric acid clearance and inulin clearance, each animal was anesthetized with pentobarbital sodium, and canulae were placed into the right femoral artery (for blood collection), left femoral vein (for drug infusion), and urinary bladder (for urine collection) of each animal. 60% Urethane was subcutaneously administered to each animal at a dose of 2 ml/kg body weight and then 1.7% potassium oxonate/1.5% inulin/4% mannitol/0.9% saline solution was intravenously administered. After that, 0.5% pottasium oxonate/4% mannitol/1.5% inulin/0.9% saline was infused to each animal at a flow rate of 0.05 ml per minute on a hot plate kept at 30 °C. Thirty minutes later, 0.9% saline was intraperitonealy administered at 4 ml/kg body weight. After the equilibrium for another 30 minutes, arterial blood (0.2 ml each) samples were collected 6 times at 20 minute interval and five 20-minute urine samples were collected. Immediately after the collection of every blood sample, the serum was separated therefrom, and the serum samples and the urine samples were stored in a refregirater.

Immediately after the first collection of the urine sample, the test compound suspended in 1% gum arabic was intraperitoneally administered at 2 ml/kg body weight.

Uric acid both in the serum and in the urine was quantitatively analyzed by the method of Yonetani et al. [Yonetani, Y.; Ishii, M.; Iwaki, K., Japanese J. Pharmacology 30, 829 - 840 (1980).] Inulin was also done substantially by the method of Vurek's and Pegram's [Vurek, G.G., Pegram, S.E., Anal.Biochem., 16, 409 - 419 (1966)]. In order to analyze uric acid, 0.2 ml of diluted solution of deproteinized serum or urine was admixed with 2.5 ml of 0.4% dimedon/orthphosphoric acid solution and the resulting mixture was heated in a hot bath for 5 minutes. The mixture was then cooled in ice-cold water and the fluorescence was measured at 400 nm in the excitation wave length at 360 nm. Control experiments were carried out using an equivalent amount of positive control compounds, ([5-chloro-3-(2-methylphenyl-4-oxo-4H-1-benzopyran-7-yl] oxy)acetic acid and benzbromarone.

b) Results

The results are listed in Table 11, showing that the ability of compounds of the present invention in

accelerating the excretion of uric acid is superior or equivalent to that of each of the control compounds.

Table 11

Example No. of Compound	dose (mg/kg)	ΔUuaV [a)] (mg/kg-min)	FEua [b)]
11	10	0.022	0.061
21	10	0.046	0.110
22	10	0.029	0.128
23	10	0.051	0.160
24	10	0.024	0.096
25	10	0.043	0.088
30	10	0.036	0.128
33	50	0.047	0.142
34	10	0.040	0.096
49	10	0.082	0.182
54	10	0.039	0.129
61	25	-0.006	0.103
control [c)]	10	---	0.081
control [d)]	10	0.068	0.125

a) Increment of urinary uric acid was calculated by subtracting the control value from the mean value of four measurements after the administration of test compound.
b) Increment of fractional excretion of uric acid [Uric acid clearance/inulin clearance (i.e., glomerular filtration rate)] was calculated by subtracting the control value from the mean value of four measurements after the administ ation of test compound.
c) ([5-chloro-3-(2-methylphenyl)-4-oxo-4H-1-benzopyran-7-yl]oxy)acetic acid
d) Benzbromarone

Experiment 2

Evaluation of xanthine oxidase inhibition activity

A mixture of 0.05 M phosphate buffer (pH = 8, 2 ml), 5.0×10^{-4} M xanthine solution (0.5 ml), and an aqueous solution of a test compound (0.3 ml) was charged in a cell for the spectrophotometer. An aqueous solution of xanthine oxidase (200 times dilution, Böelinger Manheim, milk xanthine oxidase) (0.2 ml) was added to the mixture. The absorbance at 293 nm was measured before, and 10 minutes after, the addition of xanthine. The increase in the two measurements is attributable to the amount of synthesized uric acid. A control experiment was carried out using water instead of the test compound solution. The 50% inhibition rate (IC_{50}) was determined by assuming the increment obtained in the control trial to 100.

The results are shown below:

Test compound	IC_{50} (M)
Compound prepared in Example 21:	6.5×10^{-5}
Allopurinol :	1.6×10^{-6}

The results of Experiments 1 and 2 demonstrate that the compounds of the present invention can

accelerate the excretion of uric acid and also inhibit the biosynthesis of uric acid through xanthine oxidase inhibition activity.

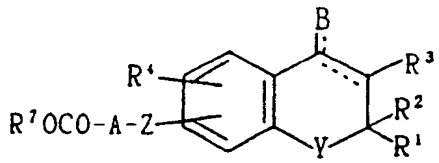
Therefore, the compounds of the invention are effective for the treatment of various disorders associated with elevated uric acid levels, including hyperuricemia, gout, ischemic cardiac diseases, cerebrovascular diseases, and the like.

For the treatment or prophylaxis of the diseases noted above, a selected compound of the formula (I) is administered to a patient suffering from any of these disorders in an amount effective to reduce uric acid levels or treat said disorders.

The compounds may be administered either orally or parenterally in the form of an appropriate pharmaceutical composition. The compositions can be in the form of tablets, granules, fine granules, powders, capsules, injectable solutions (for intravenous or intramuscular injection), and the like. The daily oral dosage for adult can be from about 0.5 to about 300 mg/kg, preferably about 5 to about 100 mg/kg, while the daily parenteral dosage can range from about 0.15 to about 100 mg/kg, preferably about 1 to about 50 mg/kg. The dose can be administered once or as several smaller dose.

Claims

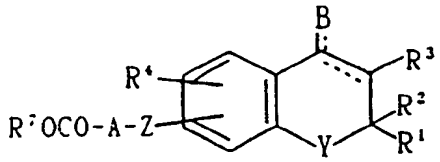
1. A compound of the formula (I):



(I)

wherein R^2 and R^2 are independently hydrogen, lower alkyl, phenyl or substituted phenyl, or R^1 and R^2 may form a four to eight-membered carbon ring together with the carbon atom to which they are attached; $R^3$is hydrogen or lower alkyl; R^4 is one or two radicals selected from a group consisting of hydrogen, halogen, nitro, lower alkyl, phenyl, substituted phenyl, $-OR^5$ and $-SO_2NR^6R^{6'}$; R^5 is hydrogen, lower alkyl, phenyl-substituted lower alkyl, carboxymethyl or ester thereof, hydroxethyl or ether thereof, or allyl; R^6 and $R^{6'}$ are independently hydrogen or lower alkyl; R^7 is hydrogen or a pharmaceutically active ester-forming group; A is a straight or branched hydrocarbon radical having one to five carbon atoms; B is halogen, oxygen, or dithiolane; Y is oxygen, sulfur, nitrogen or substituted nitrogen; Z is oxygen, nitrogen or substituted nitrogen; dotted line represents the presence or absence of a single bond.

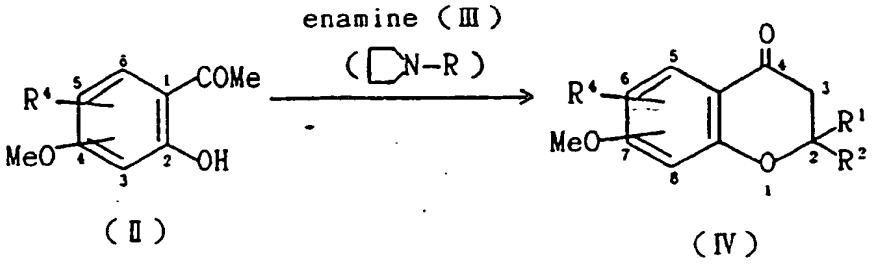
2. A process for the production of a compound of the formula (I);



(I)

wherein R^2 and R^2 are independently hydrogen, lower alkyl, phenyl or substituted phenyl, or R^1 and R^2 may form a four to eight-membered carbon ring together with the carbon atom to which they are attached; $R^3$is hydrogen or lower alkyl; R^4 is one or two radicals selected from a group consisting of hydrogen, halogen, nitro, lower alkyl, phenyl, substituted phenyl, $-OR^5$ and $-SO_2NR^6R^{6'}$; R^5 is hydrogen, lower alkyl, phenyl-substituted lower alkyl, carboxymethyl or ester thereof, hydroxethyl or ether thereof, or allyl; R^6 and $R^{6'}$ are independently hydrogen or lower alkyl; R^7 is hydrogen or a pharmaceutically active ester-forming group; A is a straight or branched hydrocarbon radical having one to five carbon atoms; B is halogen, oxygen, or dithiolane; Y is oxygen, sulfur, nitrogen or substituted nitrogen; Z is oxygen, nitrogen or substituted nitrogen; dotted line represents the presence or absence of a single bond. comprising:

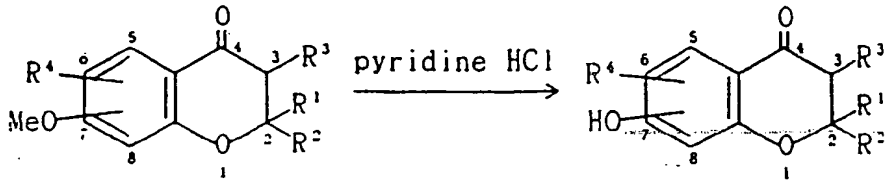
(a) Reacting a compound of the formula (II) with an enamine (III) to produce a compound of the formula (IV):



(Ⅱ) (Ⅳ)

wherein R is a 4-8 membered carbon ring having a double bond at the 1,2-position or $-C(Ph)=CH_2$ and R',R^2 and R^4 are as defined above;

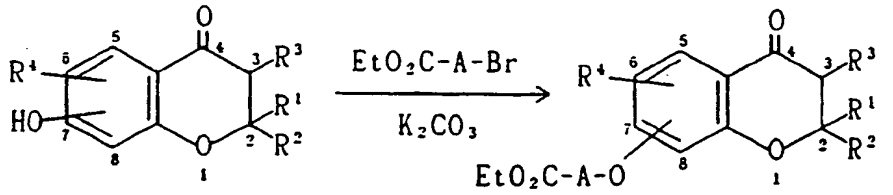
(b) Reacting said compound of the formula (IV), wherein said compound is optionally substituted by a lower alkyl group ($-R^3$) at the 3 position, with pyridine hydrochloride to produce a compound of the formula (V):



(Ⅳ) (Ⅴ)

wherein R^1,R^2,R^3 and R^4 are as defined above; and

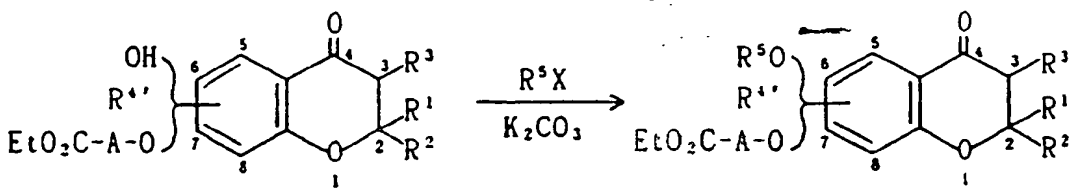
(c) Reacting said compound of the formula (V) with an ethyl ester of a halogenated carboxylic acid of the formula Et O_2 C-A-Br to produce a compound of the formula (VI):



(Ⅴ) (Ⅵ)

wherein R^1,R^2,R^3 and R^4 are as defined above:

3. A process as claimed in claim 2 wherein the resulting compound is a compound of the formula (VI′) and which further comprises reacting said compound of the formula (VI)′ with a compound of the formula R^5X to produce a compound of the formula VII:

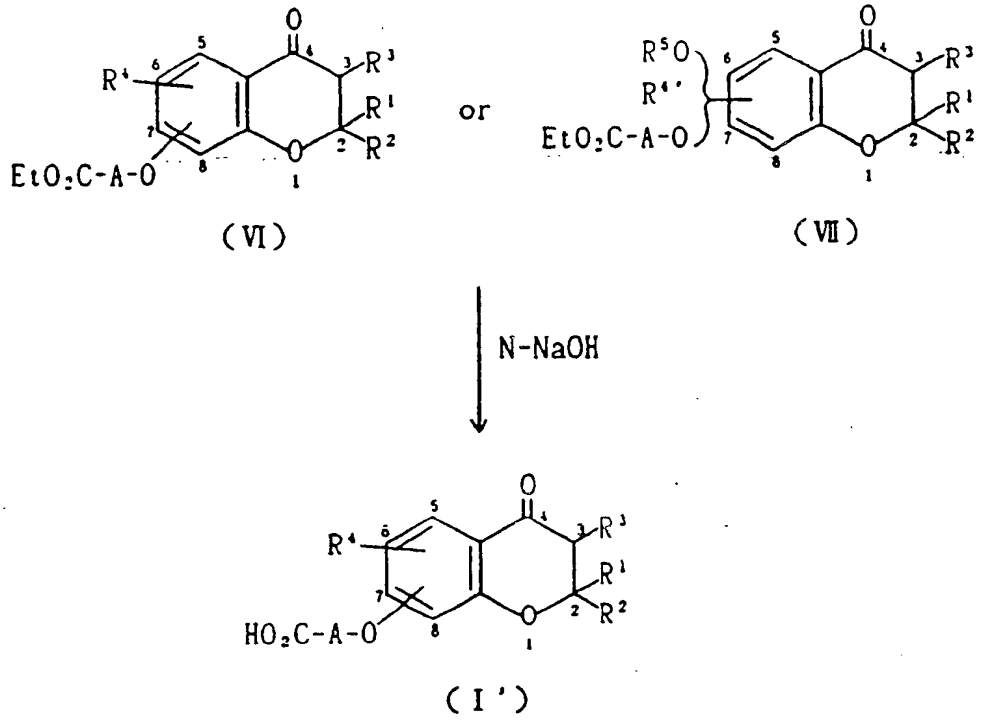


(Ⅵ') (Ⅶ)

wherein R^1,R^2,R^3,R^5 and A are as defined in to in claim 1, and $R^{4'}$, is the same as R^4 except that at least

one of the radicals is a hydroxyl group.

4. A process as claimed in claim 2 or claim 3 wherein the resultant compound (VI) or (VII) is reacted with N-NaOH to produce a compound of the formula (I'):

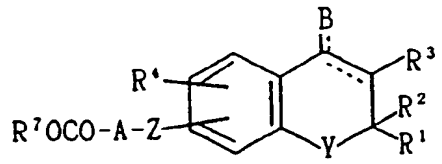


(VI) (VII)

(I')

wherein R^1,R^2,R^3,R^4,$R^{4'}$,R^5 and A are as defined in claim 2.

5. A pharmaceutical composition for the treatment or prophylaxis of hyperuricemia comprising a compound of the formula (I):

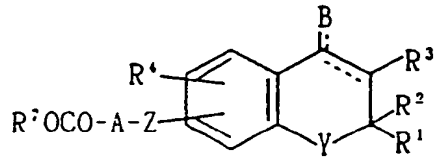


(I)

wherein R^2 and R^2 are independently hydrogen, lower to alkyl, phenyl or substituted phenyl, or R^1 and R^2 may form a four to eight-membered carbon ring together with the carbon atom to which they are attached; $R^3$is hydrogen or lower alkyl; R^4 is one or two radicals selected from a group consisting of hydrogen, halogen, nitro, lower alkyl, phenyl, substituted phenyl, $-OR^5$ and $-SO_2NR^6R^{6'}$; R^5 is hydrogen, lower alkyl, phenyl-substituted lower alkyl, carboxymethyl or ester thereof, hydroxethyl or ether thereof, or allyl; R^6 and $R^{6'}$ are independently hydrogen or lower alkyl; R^7 is hydrogen or a pharmaceutically active ester-forming group; A is a straight or branched hydrocarbon radical having one to five carbon atoms; B is halogen, oxygen, or dithiolane; Y is oxygen, sulfur, nitrogen or substituted nitrogen; Z is oxygen, nitrogen or substituted nitrogen; dotted line represents the presence or absence of a single bond, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

6. A pharmaceutical composition as claimed in claim 5 which is in unit dosage form.

7. The use of a compound of the formula (I):

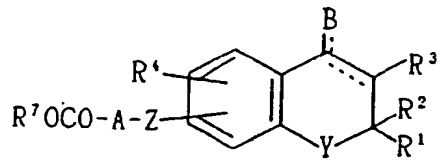


(I)

wherein R^2 and R^2 are independently hydrogen, lower alkyl, phenyl or substituted phenyl, or R^1 and R^2 may form a four to eight-membered carbon ring together with the carbon atom to which they are attached; $R^3$is hydrogen or lower alkyl; R^4 is one or two radicals selected from a group consisting of hydrogen, halogen, nitro, lower alkyl, phenyl, substituted phenyl, $-OR^5$ and $-SO_2NR^6R^{6'}$; R^5 is hydrogen, lower alkyl, phenyl-substituted lower alkyl, carboxymethyl or ester thereof, hydroxethyl or ether thereof, or allyl; R^6 and $R^{6'}$ are independently hydrogen or lower alkyl; R^7 is hydrogen or a pharmaceutically active ester-forming group; A is a straight or branched hydrocarbon radical having one to five carbon atoms; B is halogen, oxygen, or dithiolane; Y is oxygen, sulfur, nitrogen or substituted nitrogen; Z is oxygen, nitrogen or substituted nitrogen; dotted line represents the presence or absence of a single bond, in the manufacture of a medicament for the treatment or prophylaxis of hyperuricemia.

Claims for the following Contracting States: ES, GR

1. A process for the production of a pharmaceutical preparation for use in the treatment or propylaxis of hyperuricemia which comprises admixing a pharmaceutically effective amount of at least one compound of the formula (I):

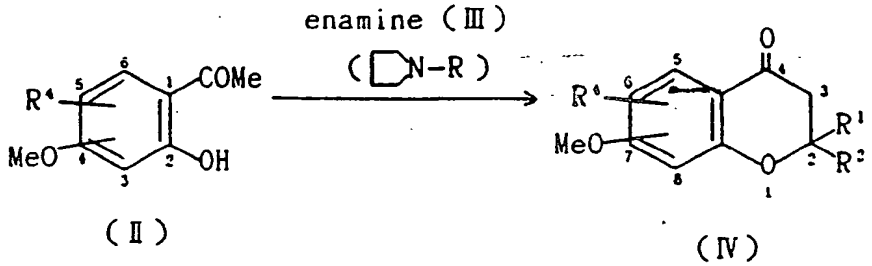


(I)

wherein R^2 and R^2 are independently hydrogen, lower alkyl, phenyl or substituted phenyl, or R^1 and R^2 may form a four to eight-membered carbon ring together with the carbon atom to which they are attached; $R^3$is hydrogen or lower alkyl; R^4 is one or two radicals selected from a group consisting of hydrogen, halogen, nitro, lower alkyl, phenyl, substituted phenyl, $-OR^5$ and $-SO_2NR^6R^{6'}$; R^5 is hydrogen, lower alkyl, phenyl-substituted lower alkyl, carboxymethyl or ester thereof, hydroxethyl or ether thereof, or allyl; R^6 and $R^{6'}$ are independently hydrogen or lower alkyl; R^7 is hydrogen or a pharmaceutically active ester-forming group; A is a straight or branched hydrocarbon radical having one to five carbon atoms; B is halogen, oxygen, or dithiolane; Y is oxygen, sulfur, nitrogen or substituted nitrogen; Z is oxygen, nitrogen or substituted nitrogen; dotted line represents the presence or absence of a single bond, with one or more pharmaceutically acceptable carriers, diluents or excipients.

2. A process as claimed in claim 1 wherein said compound is produced by a process comprising:

(a) Reacting a compound of the formula (II) with an enamine (III) to produce a compound of the formula (IV):

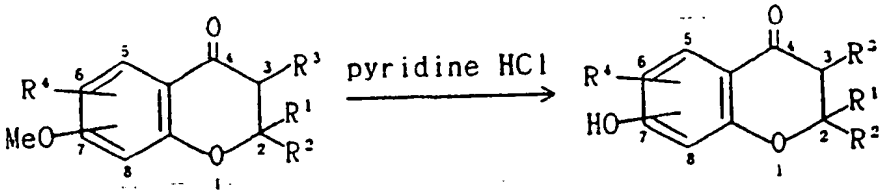


(Ⅱ) (Ⅳ)

wherein R is a 4-8 membered carbon ring having a double bond at the 1,2-position or $-C(Ph)=CH_2$ and R^1,R^2 and R^4 are as defined above;

(b) Reacting said compound of the formula (IV), wherein said compound is optionally substituted by a

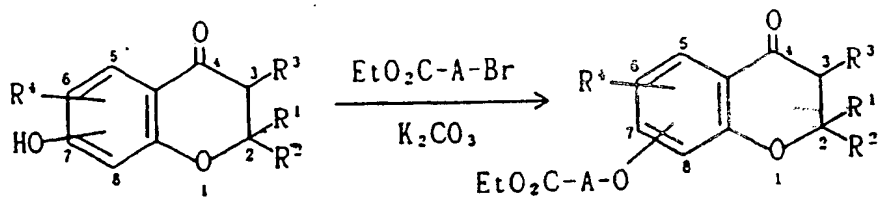
lower alkyl group (-R^3) at the 3 position, with pyridine hydrochloride to produce a compound of the formula (V):



(IV) (V)

wherein R^1,R^2,R^3 and R^4 are as defined above; and

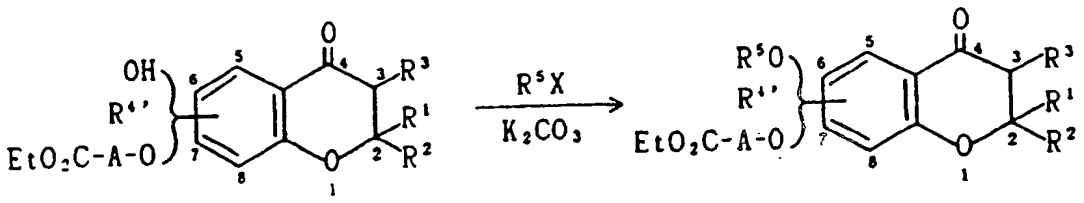
(c) Reacting said compound of the formula (V) with an ethyl ester of a halogenated carboxylic acid of the formula Et O_2 C-A-Br to produce a compound of the formula (VI):



(V) (VI)

wherein R^1,R^2,R^3 and R^4 are as defined above:

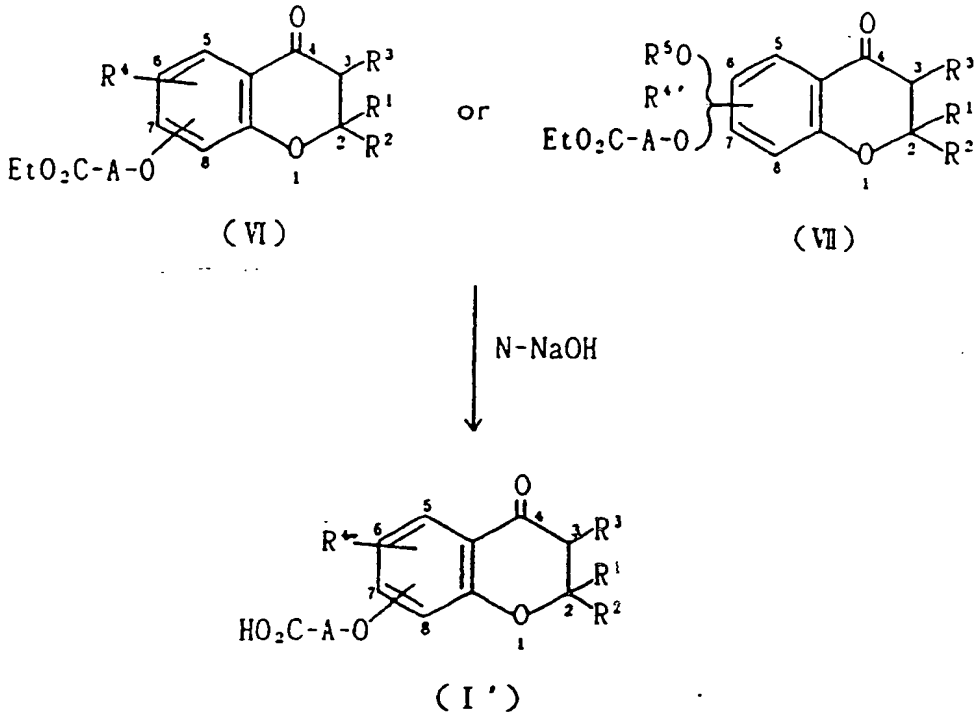
3. A process as claimed in claim 2 wherein the resulting compound is a compound of the formula (VI′) and which further comprises reacting said compound of the formula (VI)′ with a compound of the formula R^5X to produce a compound of the formula VII:



(VI′) (VII)

wherein R^1,R^2,R^3, R^5 and A are as defined in in claim 1, and $R^{4'}$ is the same as R^4 except that at least one of the radicals is a hydroxyl group.

4. A process as claimed in claim 2 or claim 3 wherein the resultant compound (VI) or (VII) is reacted with N-NaOH toproduce a compound of the formula (I′):



(VI) (VII)

(I')

wherein R^1,R^2,R^3,$R^{4'}$,R^5 and A are as defined in claim 1.

5. A process as claimed in any one of claims 1 to 4 wherein the pharmaceutical preparation is formed into a unit dosage form.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 30 8421

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	DE-A-2 535 338 (BAYER) * Pages 1-6,15,20; page 21, example 27; claims *	1-7	C 07 D 311/22 C 07 D 311/96 C 07 D 335/04
X	EP-A-0 248 420 (DAIICHI SEIYAKU) * Claims *	1,2,5-7	C 07 D 221/20 A 61 K 31/35 A 61 K 31/38
X	FR-A-2 148 363 (FERLUX) * Claims *	1,2,5-7	A 61 K 31/47
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 24, 1981, pages 408-428, Washington, US; G.E. DuBOIS et al.: "Dihydrochalcone sweeteners. A study of the atypical temporal phenomena" * Page 408; page 412, line 10; page 413, column 2; pages 416,421 *	1,2	
X	CHEMICAL ABSTRACTS, vol. 86, 1977, page 525, abstract no. 43585n, Columbus, Ohio, US; F. EIDEN et al.: "Studies on pyrones and pyridones. 60. Tetrahydrobenzodipyrandiones and tetrahydrobenzodipyrans", & ARCH. PHARM. (Weinheim, Ger.) 1976, 309(7), 529-37 * Abstract *	1	
X	LIEBIGS ANN. DER CHEMIE, 1980, pages 2021-2030, Weinheim, DE; C. SCHMIZ et al.: "Hexahydrobenzotripyrane" * Page 2021; page 2023, line 13 *	1	
X	CHEMICAL ABSTRACTS, vol. 92, 1980, page 783, abstract no. 41910q, Columbus, Ohio, US; F. EIDEN et al.: "Studies on pyran derivatives. Part 79. Ring cleavage of chromanones by oxidation with hydrogen peroxide-perchloric acid", & ARCH. PHARM. (Weinheim, DE) 1979, 312(9), 741-6 * Abstract *	1	

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TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 D 311/00
C 07 D 335/00
C 07 D 221/20
C 07 D 495/10

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	30 November 90	FRANCOIS J.C.L.

CATEGORY OF CITED DOCUMENTS

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EUROPEAN SEARCH REPORT

Application Number

EP 90 30 8421

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	GB-A-1 067 986 (MERCK) * Pages 1,2,4,7; page 10, example 9; page 12, example 24; claims *	1,2,5-7	

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